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Thesis
The Parathyroid Glands

by
Mildred Geneva Gray

(B.S. in Ed., Boston University, 1928)

submitted in partial fulfillment
of the

requirements for the degree

of

Master of Arts

1933

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Table of Contents

Introduction	6
The Ductless Glands	6.
Aim of Thesis	7
Methods of Endocrine Study	8
Objections to Certain Methods in Studying Parathyroids	9
History of the Parathyroids and Related Research	11
Before Discovery of the Glands	11
The Pathognomonic Signs of Tetany	11
Investigations Subsequent to 1880	13
Table 1 - Précis of Parathyroid History	17
Anatomy of the Parathyroid Glands	18
General Appearance	18
Shape and Color	18
Size	18
Number of Glandules	19
Accessory Tissue	20
Table 2 - Accessory Parathyroid Glandules	22
Table 3 - Terminology of Parathyroid Literature	23
Figure 1 - The Thyroids and Parathyroids of Man	24
Figure 2 - Specimen A to show relative Size	25
Figure 3 - Specimen B to show relative Size	26
The Embryology of the Parathyroids	27
Relation to Thyroid and Thymus Glands	27
Development in Lower Animals	28
Figure 4 - The Embryology of the Branchial Pouches	30

Appendix A

Page 10 of 10

1. The first part of the

2. The second part of the

3. The third part of the

4. The fourth part of the

5. The fifth part of the

6. The sixth part of the

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16. The sixteenth part of the

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18. The eighteenth part of the

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20. The twentieth part of the

21. The twenty-first part of the

22. The twenty-second part of the

23. The twenty-third part of the

24. The twenty-fourth part of the

The Blood Supply of the Parathyroids	31
Arterial Supply	31
Contact of Vessels with Secretory Cells	32
The Lymphatic System	33
Venous Drainage	33
Vascular Landmarks	34
The Parathyroids and the Nervous System	35
Vasomotor Character of Innervation	35
Effect of Innervation on Secretion	36
Effect of Secretion on Nervous Tissue	36
Cell Changes in Nervous System	37
The Microscopic Structure of the Parathyroids	39
Types of Cells	39
Intercellular Structures	40
Histologic Appearance In Hypertrophic Conditions	40
Comparative Histology	42
Figure 5 - Microphotograph of Normal Parathyroid Tissue	44
The Comparative Anatomy of the Parathyroids	45
In Class Amphibia	46
In Class Aves	46
The Mammalian Parathyroids	47
In Domesticated Animals	48
Pathological Changes Affecting the Parathyroid Glands	50
Increase of Colloid	50
Haemorrhage	50
Infiltration of Fat	51
Fibrotic Conditions	52
Infectious Lesions	52
Neoplasms	52

1 The first part of the document
2 deals with the
3 history of the
4 The second part
5 deals with the
6 The third part
7 deals with the
8 The fourth part
9 deals with the
10 The fifth part
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94 The forty-seventh part
95 deals with the
96 The forty-eighth part
97 deals with the
98 The forty-ninth part
99 deals with the
100 The fiftieth part

The Normal Metabolism of Calcium	54
Calcium Requirements of Man	54
Circulating Calcium	54
Effect of Variations of Body Calcium Levels	55
The Absorption of Calcium and Factors which Assist	59
Effect of Sunlight on Absorption	59
Irradiation	60
Vitamin Concentrates	60
Cod Liver Oil	61
The Physiology of the Parathyroids	63
Guanidine-Intoxication Theory	63
Other Detoxication Theories	65
Influence of Acid-Base Balance in Tetany Production	69
The Parathyroids and Parathyroid Tetany	71
Constancy of Low Calcium Levels in Syndrome	71
Vital Need of Parathyroid Tissue	71
Clinical Picture During Tetany in Man	75
Neurological Effects of the Disease	76
The Signs of Tetany	77
Parathyroid Tetany of Animals (Experimental)	79
Latent Tetany	82
The Sequellae of Tetany	83
Incidence and Severity of Tetany	85
Incidence of Post Operative Tetany	85
Endemic Tetany	86
Table 4 - The Incidence of Parathyroid Tetany Following Thyroidectomy	87
The Therapeusis of Tetany Other Than with Parathormone	88

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Use of Mineral Acids and Salts	88
Thyroid Preparations	88
Administration of Calcium Compounds	89
Results Obtained from Grafted Tissue	91
Autotransplants vs. Homotransplants	92
Optimum Sites for Transplantation	93
The Secretion of the Parathyroid Glands	94
Extracts of Vassale and Berkeley-Beebe	94
Preparation by Hanson (1924)	94
Berman's Crystalline Compound (1924)	95
The Parathormone of Collip (1925)	95
Preparation	96
Chemical Structure and Properties	97
Purification	97
Tweedy's "Plasma-Calcium Raising Principle"	98
Effect of Intravenous Parathormone	99
Mode of Action of Parathormone	99
First Clinical Use	102
Use in Clinical Infantile Tetany	102
General Effect on Osseous Tissue	103
Standardization of Parathyroid Hormone	105
The Unit of Parathyroid Hormone	105
Burn's Method	105
Use of Cats (Stewart and Percival)	106
Hyperactive Conditions Involving the Parathyroids	109
von Recklinghausen's Disease	110
The Work of Erdheim	110
The Pathological Approach to Hyperparathyroidism	113

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Other Bone Diseases Associated with Parathyroid Hyperfunction	113
Effect of Increased Plasma Phosphatase	114
Giant Cell Tumors and Adenoma ^{ta}	115
Treatment of Hyperparathyroidism in Man	116
Relation of Parathyroids to Other Organs in Man	117
Possible Relation to Carbohydrate Metabolism	117
Antagonisms between Parathyroids and Other Glands	118
Relation to Gonads	118
Relation to Parkinson's Disease and Other Pseudo-Paralytic Conditions	119
Effect of Parathyroidectomy on Bile Duct and Colon	120
Summary and Conclusion	121
Appendix A - John Clarke's Description of Tetany (1815)	125
Appendix B - Description of Commercial Preparations of Parathyroid Hormone	129
Appendix C - Method for Determining Calcium in Serum and Spinal Fluid	137
Appendix D - A Case of Parathyroid Tetany Occurring after Thyroidectomy and in which Transplanted Tissue was Ineffective	139
Figure 6 - D.R. aged 14	143
Figure 7 - D.R. Demonstrating Carpal Spasm	143
Bibliography	144

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effects of the proposed project on the

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information in the attached report

of interest.

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Introduction

To Ivar Sandstrom, a Danish anatomist, belongs the distinction of having completed the chain of structures which comprises the endocrine system. It was in 1880 that he discovered the parathyroid glands and in the fifty years subsequent, masses of experimental data have been accumulated and a great amount of pertinent literature has been written. Of all this, only a single fact is generally undisputed, namely, that parathyroid tissue or its substitute is necessary to life. For every other quid there is a quo. Inevitably, the loss of the gland or cessation of its function results in death preceded by characteristic neuro-muscular symptoms.

The homeostatic activity of the parathyroid glands in calcium metabolism links them with many diseases. Annually the category grows in numbers. Deviation from the normal function in either direction is serious. Correction of hyperfunction is probably attended with more difficulty than underfunction for the latter state can be controlled by administration of the absent or deficient hormone.

The definition of a ductless gland deserves momentary attention. That of Biedl (21) in 1913 seems to epitomize best the nature of the endocrines, namely, ".....glands conforming to definite histological types with structures peculiar to each gland, manufacturing

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specific chemical combinations and delivering these to the organism through blood and lymph channels, producing by means of infinitesimal quantities of these substances certain definite effects upon the function of other body cells without furnishing material for cell building....."

The purposes of these gland elaborated secretions are not identical. A gland is not a true endocrine until its ability to elaborate a secretion has been demonstrated. The process of formation is chemical but the action is not a true chemical reflex. Rather it is the stimulation of one organ by the product of another. The action may be pressor, depressor, antitoxic, homeostatic or coordinatory but a chemotactic effect can be seen to result in all organisms, from lowest to highest, wherever a true endocrine structure can be identified. (Starling, 180)

To the secretion, Starling's term, "hormone" (Gr. $\delta\rho\mu\omega$, I stir up) is well applied. It is more descriptive than that which it replaced, the "secretion interne" of Claude Bernard.

In this paper, an attempt will be made to review the most salient information available and to evaluate it. The parathyroid apparatus seems especially noteworthy because of its influence on the normal and the morbid metabolism of calcium and thus indirectly on the relation it bears to heightened and diminished states of neuro-muscular excitability. In addition, the current

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attempts to link the calcium ion with the states of sympatheticotonia and vagotonia and with changes in personality seems to warrant inquiry into the fundamental mechanisms underlying the concepts.

Whether we accept or reject such theories, we shall see that a balance of the endocrine system is necessary to the harmonious integration of the sympathetic and autonomic nervous systems. As Paton (157) phrases it, ".....there must be coordination by the glands because of their effect on personality and regulation of bodily activity. This is necessary to an orderly development of the body in early life and to harmonious adjustment of the various activities of maturity."

There are essentially three states of endocrine activity which are of interest in investigating function (a) the normal, (b) hypofunction, and (c) hyperfunction. Hypofunction may be produced artificially by excision or destruction of the gland. Hyperfunction may be produced by transplantation, feeding of the gland substance or by injection of a potent extract (organotherapy or opotherapy of Brown-Séquard). Occasionally an animal is seen with a congenital lack of some gland but as far as can be learned there has never been seen the anomaly of aparathyreosis in man or in any species where the gland is normally found. This is not strange when the vital character of its function is considered. The parathyroid glands have been found even where the thyroid is congenitally lacking and this fact may be cited to demonstrate the functional distinctness of each.

The parathyroids may be destroyed by disease, trauma, crushing, excision or arterial ligation. In every case the consequences are swift and serious. Hyperactivity eventually becomes equally serious to the animal suffering it. The cause of the increased function may be a neoplasm, hypertrophy, accessory tissue, neural stimulation, implantation of additional tissue or administration of gland substance,

Each of the above cited factors has been utilized in the study of the parathyroid glands. Clinical observation yields some information. Data gathered after extirpation are to be preferred to those obtained following pathological destruction of the glands since in the latter case, localization of the lesion is difficult; and extraneous, uncontrolled factors complicate the situation under investigation. Postmortem examinations, inhibition of tissue growth and destruction by Röntgen ray are productive in some measure of information relative to structure but give little light as to function.

There is a marked objection to the data gathered following surgical extirpation because of the accompanying shock, derangement of circulation and nerve injury. Experimental study is further complicated by the ability of higher animals to regenerate lost tissue, and the characteristic of some organs to assume the duties of a missing part. Those who question the functional distinctness of the components of the so-called thyroid apparatus give considerable credence to this possibility.

The specificity of the secretion of the parathyroid glands is not limited to a single species. Therefore a comparison can be reasonably be made of various data derived experimentally by the use of different animals to demonstrate the same hypothesis of glandular function.

The Committee on the Study of the
History of the State of New York
has the honor to acknowledge the receipt
of the report of the Committee on the
History of the State of New York
and to express its appreciation of the
work done by the Committee.

The History of the Parathyroid Glands and Related Research

Prior to 1880 when Sandstrom's careful anatomical and histological studies appeared in print, there had been notations of the occurrence of tetany, especially of the infantile and gastric type. Clarke, in 1815, had described spasms of the glottis and extremities in children but considered them idiopathic. (See Appendix A) In 1824, Sir Astley Cooper described the fatal effects of thyroidectomy in dogs. Schiff, Billroth and von Eiselsberg, in 1856, 1880 and 1890 respectively, corroborated Cooper's finding. In the light of our present knowledge, we can ascribe death to the simultaneous removal of the parathyroid glands. If the thyroids alone had been excised a progressive cachexia would have resulted. The rapidly terminating exhaustion and convulsions were due to the loss of associated parathyroids. Both Steinheim (1830) and Corvisart (1852) described tetany. Weiss, in 1880, assigned the name which has persisted.

In 1873, Erb studied the hyperexcitability of the motor nerves in the tetany of infants. The nerves were especially responsive to galvanic current. At the present time, the reaction is called "Erb's sign". Hoffman, in 1888, claimed a correspondingly low threshold of response in the sensory group which if present at all is comparatively rare. In 1875, Trousseau noted the peculiar contracture of hands and feet during a tetanic

seizure. He called the carpal spasm "main d'accoucheur". It is now commonly alluded to by his surname. Chvostek, père, noted in 1878 that during tetany he could consistently elicit a lively response when he tapped the motor nerves of the face with a percussion hammer or when he merely stroked the skin over the facial nerve with his finger nail. The Chvostek sign is considered to be good evidence of latent tetany even when other symptoms are lacking.

All these findings were made before 1880. In that year, Ivar Sandstrom published a classic paper in Schmidt's Jahrbucher describing the constancy of parathyroid bodies in fifty post mortem examinations in man. He found parathyroid bodies in the rat, rabbit, ox and horse. In 1863, von Virchow had seen small, round, pea-shaped lumps in the connective tissue near the thyroid but had considered them to be lymph nodes or undeveloped embryonic thyroid tissue.

Kaydi in 1881 and Masselung in 1882 duplicated the work of Sandstrom. Rogowitz in 1888 found the parathyroid glands in man. He referred to them as "restes embryonnaires" and considered them, like von Virchow, as parts of the thyroid gland in the process of development.

Once the scientific world became aware of the new gland in the cervical region of mammals and the higher vertebrates little effort was spared in the attempt to wrest all possible knowledge from the parathyroids. Ten years had passed before they were adequately recog-

nized and in that time Sandstrom had been forgotten. Gley (80) in the period between 1890 and 1897 demonstrated that tetany was associated with the removal of the parathyroid glands. He performed a thyroidectomy without disturbing the parathyroids and noted no tetany after operation. When a parathyroidectomy was done later on the same animals, tetany and death ensued. Thus he proved that there were two distinct functioning entities in the "thyroid apparatus". His results were published originally in fifteen papers in the "Comptes Rendu Hebdomadaires de Societe de Biologie de Paris". With Sandstrom's report they represent the most classic literature in the field.

Horsley working in England noted consistently a tremor in monkeys after thyroidectomy but did not associate it with the parathyroids. About the same time (1891) von Recklinghausen, a pupil of von Virchow described the disease which bears his name. Many years elapsed before 1929 when Mandl associated von Recklinghausen's disease with parathyroid hyperfunction.

By 1895, Kohn had placed the anatomy and histology of the glands on a functional basis and had differentiated them from the neighboring thyroids. In the course of his work he described the internal glandules for the first time. An autacoid was first intimated to be present in 1898 when Moussu affirmed that he had arrested postoperative tetany in dogs by parenteral administration of an extract of equine glands.

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Two Italian physiologists, Vassale and Generali, demonstrated in 1896 that parathyroidectomy alone led to tetany where thyroidectomy alone was followed by cachexia. This served to corroborate the earlier work of Gley and to turn the attention of workers of the time from anatomy and histology to functional studies. Vassale and Generali applied their findings to man but in this respect their work was not taken seriously because of the rarity of either operation at the time.

With the turn of the century, interest was focussed on the physiology of tetany but the work was obscure and largely speculative until MacCallum and Voegtlin (133) in 1909, by actual analysis proved the calcium of the blood to be low when tetany supervened. That calcium salts were palliative in tetany was soon proved to be more than an hypothesis. For the next twenty years, work progressed toward relating tetany to low blood calcium and to developing therapeutic rationales which utilized calcium preparations and high calcium diets.

Many theories of function were evolved in the first two decades of the twentieth century. All but the calcium level-maintenance hypothesis have fallen into disrepute. Vincent and Jolly (201) in 1905 expressed belief in the assumption of function by the thyroid gland after parathyroidectomy. The only other theory to have much support was that referred to as the "toxin" theory of Berkeley and Beebe. They believed tetany to be due to deranged metabolism and the resultant storage of toxins

The first thing I noticed when I stepped out of the car was the cold. It was a sharp contrast to the warm blanket of the car. I looked up at the sky, which was a pale, hazy blue. The air was still, and the silence was broken only by the distant hum of traffic. I took a deep breath, feeling the cool air fill my lungs. The ground beneath my feet was wet and slick, reflecting the light from the sky. I walked slowly, my steps echoing on the pavement. The world around me seemed to be holding its breath, waiting for something to happen. I felt a sense of anticipation, a mix of excitement and nervousness. The day was just beginning, and I knew that whatever was to come, it would be unforgettable.

in the blood. In 1909, they had found guanidine in excess of the normal concentration in the urine of parathyroidectomized dogs. In 1913, Koch obtained like results. Paton and others working in Edinburgh duplicated the symptoms of tetany by the injection of guanidine compounds. Later it will be seen that the objections to the toxin theory were of sufficient magnitude to cause it to be discarded.

Little was done experimentally with reference to the secretion of the gland until 1909. In 1905, Vassale had claimed to have prepared an extract, parathyroidin, which was effective in parathyroid tetany of man. Four years later, Berkeley and Beebe extracted a nucleoprotein from bovine glands by acetic acid hydrolysis which prevented and arrested tetany in dogs after removal of the parathyroids. In the succeeding years up to 1924, many such preparations were used in various countries but none was standardized or made uniform. In the main, they consisted of desiccated or preserved gland substance.

In 1924, Hanson (98,99,100) prepared an acid hydrolysate of bovine glands which he standardized and used effectively in man. However, his work was not published until after that of Collip in 1925 and rules of priority of publication give full credit to the latter for isolating and preparing the active principle of the parathyroid gland. It is frequently called Parathormone. The control of tetany and regulation of the blood calcium level ~~are~~

its chief properties.

Since 1925 experimental work on the parathyroid glands has been clinical in nature. Elaborate studies of the metabolism in anomalous conditions have been made. Especial attention has been given to bone disorders which result from hyperparathyroidism. In Austrian, German and French laboratories, the popular phase of parathyroid research is the investigation of osteitis fibrosa cystica, osteoporosis and osteomalacia. In England and America, the use of parathyroid secretion in diseases not primarily associated with the parathyroid glands is receiving careful study.

TABLE ONE

/
 PRÉCIS OF PARATHYROID HISTORY

- 1815 - Clarke described spasms of glottis and extremities
- 1863 - von Virchow noted parathyroid glands but attached no importance
- 1873 - Erb described phenomenon of hyperexcitability
- 1875 - Trousseau's sign described
- 1878 - Chvostek, père, described response of facial nerve in tetany
- 1880 - Sandstrom noted new gland in cervical region of man and higher vertebrates
- 1891 - Gley demonstrated thyroid and parathyroid glands to be separate entities
- 1895 - Kohn described internal pair of glands
- 1896 - Vassale and Generali demonstrated that parathyroidectomy alone caused tetany
- 1909 - MacCallum and Voegtlin related calcium and tetany with the parathyroid glands
- 1909 - Berkeley and Beebe advanced toxin theory and prepared extract of bovine glands which arrested and prevented tetany
- 1924 - Hanson prepared acid hydrolysate of bovine glands which was active principle of the parathyroids
- 1925 - Collip prepared pure hormone and published report
- 1929 - Mandl linked von Recklinghausen's disease with the parathyroids

THE HISTORY OF THE UNITED STATES

1. The first part of the book is devoted to the history of the United States from the discovery of the continent to the establishment of the first colonies.
2. The second part of the book is devoted to the history of the United States from the establishment of the first colonies to the American Revolution.
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The Anatomy of the Human Parathyroid Glands

The structure of the human parathyroid glands is that of the most compact and vascular organ in the body. (Scharpey-Schafer, 175) There is much connective tissue but it differs in quality in various parts of the gland, being especially dense near the cortex of the parathyroid.

A single glandule is very similar in shape and appearance to a lymph node and is quite often mistaken for the latter. The color of the parathyroids varies from pale grey white to deep red brown. The frequent yellow tinge is due to the lipoid material contained in the gland. Gray (83) describes the appearance as that of oval discs with a flat, pyriform outline.

The average measurements are a length of 6-7 mm. , a width of 2 -4 mm., and a thickness of 1.5 - 2 mm. The width is the most uniform measurement to be found in an unselected series of specimens. Ochsner and Thompson (153) alone contradict the rule of bilateral symmetry observed by many autopsists.

The glands are less transparent than lymph nodes and through the slight opacity of the capsule can be seen a delicate tracery of veins. Fixation in alcoholic formalin enhances a glistening effect seen in situ. This appearance ^{of the gland} after a short time in the fixing fluid can be used presumptively to differentiate the parathyroids and questionable bits of lymphatic tissue and fat.

THE HISTORY OF THE UNITED STATES

OF THE UNITED STATES OF AMERICA

FROM THE FIRST SETTLEMENTS TO THE PRESENT TIME

BY

JOHN F. JOHNSON

OF THE UNIVERSITY OF CHICAGO

AND

OF THE UNIVERSITY OF CALIFORNIA

AND

OF THE UNIVERSITY OF MICHIGAN

AND

OF THE UNIVERSITY OF TEXAS

AND

OF THE UNIVERSITY OF VIRGINIA

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AND

The size of the parathyroid glands is disproportionate to their importance and renders their removal difficult. (See Figure Two and Three) The only positive identification is by histologic means. In 125 autopsies, Berkeley found the maximum weight of four glands to be .3763 gms. or roughly that of a hemp seed. Recognition of the parathyroids in man in obese and atrophic conditions is extremely difficult. In children the glands can be found quite easily since they are at that stage of development comparatively free from fat and connective tissue. In locating the glands before removal it is safest to find at least four since once the field becomes blood stained, the uncertainty of complete removal is magnified.

Ordinarily there are two pairs of glandules, the posterior-superior and the inferior-anterior. The upper pair is more constantly placed in man and is at the junction of the oesophagus and pharynx, usually on the dorsal surface of the upper, pyramidal process of the thyroid gland. They may be found by following the inferior thyroid artery or the recurrent laryngeal nerve cephalad. The lower pair is variously situated and may often be found at the lower edge of the pyramidal process of the thyroid gland. Frequently the lower pair of parathyroids is placed at the lower edge or on the medial surface of the thyroid. The parathyroids have been found as low as the fourteenth tracheal ring or even attached to the phrenic nerve in man. The glands are frequently embedded

in the thyroid. The connective tissue sheath of the parathyroid glands is derived from and continuous with that of thyroid.

As the name indicates, the parathyroids bear an intimate spatial relation to the thyroid gland but otherwise are quite distinct. Many islands of parathyroid tissue are scattered through the cervical connective tissue and fat making complete parathyroidectomy almost impossible. They are a source of great uneasiness to surgeons during thyroidectomy since removal of the parathyroids inadvertently means that the patient will suffer from tetany after operation. Aberrant glandules are found often in the thoracic cavity and in the thymus gland. When found in the latter location, it is the result of embryonic compression of the branchial pouch anlagen. Canavan (39) says that accessory glandules can be found in numerical proportion to the patience and persistence of the searcher. Pepere (160) in 1906 found fewer than four glands in less than one per cent of one thousand autopsies and more than four in over thirty three per cent. When a glandule is missing it is usually replaced by a type of tissue which resembles it but which lacks its function.

Anatomical insufficiency is always accompanied by physiological insufficiency but the converse is not always true. Underfunction may be observed when the glands are intact. No good evidence exists that an animal can survive complete parathyroidectomy. There

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is only a narrow margin between the normal condition and tetany and parathyroidectomy is dangerous even if accessories were known to be present.

Table Two indicates the findings of seven workers relative to the presence of accessory glandules in man. All the findings cited were verified microscopically.

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TABLE TWO
ACCESSORY PARATHYROID GLANDULES IN MAN

Normal number - two pairs

Erdheim	8
Scharpey-Schafer	6
Zucker-Kandl	8
Getzowa	7
Thompson-Harris	5

Verified microscopically in one or
more cases

Sandstrom consistently found two per side

Von Verebely found four glands in 108 of 136 cases

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DEPARTMENT OF CHEMISTRY

PHYSICAL CHEMISTRY

LECTURE NOTES

BY

PROFESSOR

JOHN D. COLEMAN

CHICAGO, ILLINOIS

1960

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TABLE THREE

TERMINOLOGY USED IN PARATHYROID LITERATURE

Sandstrom	Glandulae parathyroideae
Gley	Glandules thyroïdiennes
Hofmeister	Nebenschilddrüsen
Zielinska	Nebendruesen
von Jacoby and Blumreich	Accessorische Schilddrüsen
von Tourneux and Verdun	Glandules thymiques
Kohn	Epithelkoepcherchen
von Verebely	Branchiale Koepcherchen
English and American writers	Parathyroid glands

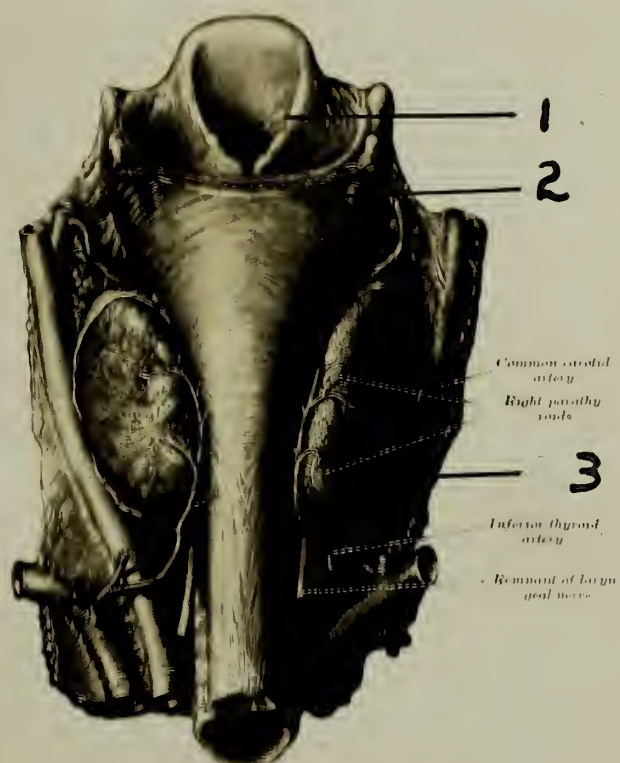


Fig. 1177. Parathyroid glands. (Halsted and Evans.)

**Figure One The Thyroid and Parathyroid Glands
in Man**

(From Gray's Anatomy after Halsted and Evans)

1. Trachea
2. Oesophagus
3. Thyroid Gland

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Figure Two Specimen (A) to illustrate the relative size of thyroid and parathyroid glands in man

(Parathyroids enclosed by circles)

Male, aged 70, Foxboro State Hospital

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Actual Size

Figure Three Specimen (B) to illustrate the relative size of thyroid and parathyroid glands in man

(Parathyroids enclosed by circles)

Male, aged about 40

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The Embryology of the Parathyroid Glands

When the relation of the component parts of the human thyroid apparatus is traced through the course of their development, many anomalies of the thyroid, thymus and parathyroid glands are explained. The accompanying drawing of the branchial pouches (Figure Four) shows the original site of each organ. The thyroid gland arises from a median body at the root of the tongue and from two lateral bodies which begin as small buds on either side of the posterior wall of the fourth branchial cleft. The thymus grows from two epithelial invaginations of the third branchial cleft which extend downward and meet to form the two lobes of this gland.

Ballantyne (8) described the parathyroids as a link binding the thyroid to the thymus and associated in the function of regulating metabolism. They arise as two separate pairs, one from the fourth and the other from the third branchial cleft. The former pair comes to lie on the dorsal surfaces of the lateral part of the thyroid and are called the superior bodies. The other pair migrate dorsally and come to rest on the lower border of the thyroid frequently being embedded there.

Kohn in 1895 used the distinguishing terms "inner" and "outer" because the glands lying most dorsally are outside the thyroid while those in the ventral position are embedded. At their first appearance, the

THE HISTORY OF THE UNITED STATES

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anlagen are mere thickenings of the entoderm.

Although the "glandulae parathyroidae IV" are from the fourth pouch they are located anterior to those referred to as "glandulae parathyroidae III" (originating in the third pouch) because in the caudal migration of the branchial derivatives, the thyroid and the "glandulae parathyroidae IV" are outdistanced. Sexual variations are unknown in the embryonic parathyroids. In the adult female, the glands are larger than those of the male and in that respect they resemble the adrenals and the pituitary gland.

If the bilateral parts of the thymus are pushed downward while developing, the parathyroids may rest on the thymus gland and become embedded there. The parathyroid may occur as high as the hyoid bone. McCarrison (143) states that he found the thymus and parathyroids to be mutually heterotopic in many cases. The observation of most writers is that the thymus is seldom displaced. Intrathymic islets of parathyroid tissue may be found but their contiguity does not mean continuity of thymus and parathyroids. Cobb (45) states that the distinction between thymus and parathyroids is never as distinct as in embryo. Gley (80) called the parathyroids "embryonic thyroid tissue" but his statement was made before he proved the glands to be functionally distinct.

Concerning the development of the parathyroids in other animals than man, Wilder⁽²¹²⁾ states: "The occurrence of post-branchial bodies is uncertain but some persons identify these with a pair of invaginations that in

mammals arise from the same region and eventually become lost in the lobes of the thyroid gland..... the so-called parathyreoid bodies."

In tadpoles, the parathyroids develop at the time when the outer gills form. The glands arise as compact buds on the ventral side of the third and fourth branchial pouches. At first there is a pedicle connecting the epithelial cell masses to the pouch but it is later absorbed. In the urodeles, parathyroid formation takes place during metamorphosis. The glands lie on or between the lateral convex sides of the aortic arches. Sometimes additional bodies occur in both places so that there are three glands per side.

The reptiles have one parathyroid body which arises from the second cleft during closure of the branchial pouches. In birds, a varying number of parathyroid glandules are found ventral to the thymus. In the chick and the duck, a third body is found which seems to arise from a fifth branchial cleft (Ochsner and Thompson, 1933).

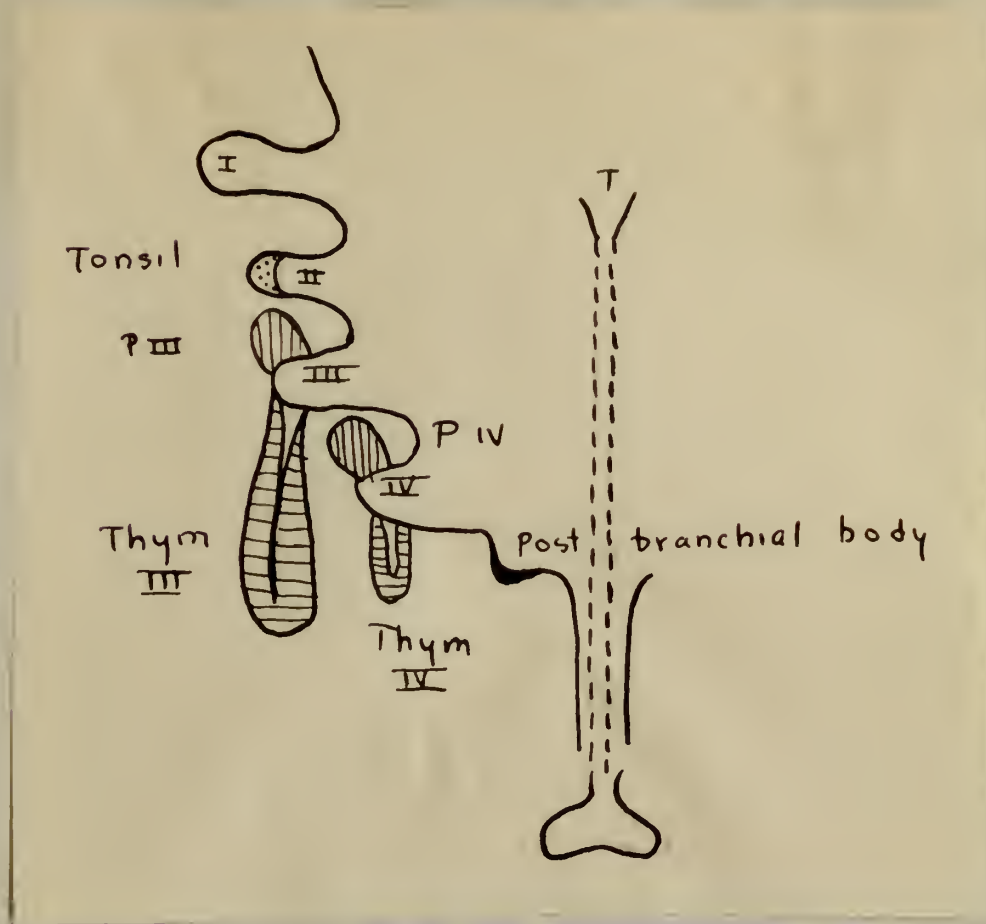


Figure Four The Embryology of the Branchial Pouches
(From Barker's Endocrinology and Metabolism)

To illustrate the origin of the branchial cleft organs
in the mammalian embryo

- | | |
|-----------------|---|
| I - IV | Branchial clefts or pouches |
| P III | Origin of lower or external parathyroids
from cephalic aspect of pouch III |
| P IV | Origin of upper or internal parathyroids
from cephalic aspect of pouch IV |
| Thym III and IV | Thymus from caudal aspect of pouch
III and IV |
| T | Thyroid |

The Blood Supply of the Parathyroid Glands

The marked vascularity of the parathyroid glands is their most unique characteristic. Scharpey-Schafer (175) described the profusion of blood vessels by saying ".....(they) consisted of special arterioles originating from the inferior thyroid artery or from an anastomic branch." These, he wrote, empty into sinusoid capillaries which ^{in turn} enter into close relation with the epithelial cells of the gland. The capillaries unite and ramose to form a complex network touching every cell of the gland.

Since the circulation is terminal, there is danger of isolation by cutting the main vessels. However, it is quite as serious to ligate the vessels as to sever them. Either may be done during thyroidectomy and tetany invariably follows. Mumford (149) used the main arteries as landmarks in locating the parathyroids. He noted the prominent anastomosing rami as early as 1908.

Crotti (58) recognized a vessel which he called the parathyroid artery but is now considered identical with the large division of the inferior artery which supplies both the inferior and superior parathyroid glands. Rarely there may be separate arteries to each glandule. These, too, anastomose considerably. Sometimes the supply is from collateral vessels, especially in the dog. The collateral vessels come directly from the posterior, running on the inner border of the thyroid gland to connect the inferior with the superior

THE HISTORY OF THE UNITED STATES

OF THE UNITED STATES OF AMERICA

FROM THE FIRST SETTLEMENTS TO THE PRESENT TIME

BY JAMES M. SMITH

OF THE UNIVERSITY OF CHICAGO

IN TWO VOLUMES. VOL. I.

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thyroid arterial system. The fine collateral circulation between the thyroid and parathyroid glands extends to the pharynx, oesophagus and trachea. Crotti further claimed that a secondary source exists which will permit ligation of the vessels from the thyroid gland without the risk of parathyroid hormone insufficiency. In view of the lack of corroboration this observation may have been based on a vascular anomaly.

The arteries enter the parathyroid at the hilum or from the capsule and break up into a plexus of capillary (sinusoidal) vessels. The network of vessels follows the fibrous tissue stroma to the periphery and becomes intimately associated with the epithelium. The contact of the vessels with the secretory cells is noteworthy and as far as can be learned is peculiar to the parathyroid glands. The small branches of the vascular system penetrate deeply into the gland, dividing and redividing until every follicle is surrounded by a framework of sinusoid capillaries with which the epithelium is in perfect contact.

The thin-walled venules retrace the course of the arterial capillaries, it is generally agreed. MacCarrison (143) disagreed with the statements that the venous system is composed of tiny vessels retracing the course of the arteries. He described them instead as large, numerous and freely communicating, leading to the

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inferior thyroid vein directly or by way of veins covering the surface of the parathyroid gland. Most anatomists agree that the veins of the parathyroid eventually empty into the jugular and innominate veins. There are no valves in the veins of the parathyroid gland.

The lymphatic drainage is free and joins the lymphatic system of the thyroid, the lymph commingling freely with the secretion from the latter organ. The lymphatic system of the thyroid is complex. The lymph spaces lie outside the peri-vascular capillaries and actually constitute peri-alveolar spaces. These join the interlobular vessels and form large trunks or plexi just under the thyroid capsule. From the plexi, two main trunks convey the secretion containing the mixed lymph, thyroxin and parathyroid hormone to the circulation via the superior and inferior deep cervical glands.

Falta and Meyers (76) emphasize the numerous, very wide capillaries between the individual cell groups and the columns of cells. It is of interest in passing to note the very scanty blood supply to the capsule itself. The few minute capillaries present there stand out in relief following ligation of the main artery in the dog. Delafield and Prudden (62) and Marine (138) speak of a few peripheral subcapsulary veins.

In man the usual method ^{employed} ~~used~~ to locate the glands is to follow the inferior thyroid artery and the recurrent laryngeal nerve. They pass in front and internal to the inferior glandules. The superior bodies are

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found at the entrance of the end branches of the inferior thyroid artery.

Taylor (187) in writing of the mode of secretion explained the proliferation of vessels by stating that each cell is in constant contact with blood and the secretion when elaborated passes into hairlike tubes leading from the numberless cavities to the venous system. Thence the vessels join the lateral part of the thyroid venous system.

The branches of the arteries are out of proportion to the size of the gland. After the main vein leaves the gland at the hilum, it maintains no further constant course.

The earliest comprehensive study of the blood supply of the parathyroids was made by Halsted and Evans (94) in 1907. Their counsel to follow the arteries in finding the glands is especially useful when they are embedded in fat. Halsted and Evans utilized injection methods and were thus enabled to note whether the arterial source was from the glandular, muscular or oesophageal branch of the thyroid artery. They also noted the scanty blood supply to the connective tissue mesh which is more marked in view of the ample supply to the secretory cells.

The Parathyroids and the Nervous System

Until 1913 there was no anatomical proof that nerves are present in the gland. It was surmised that fibers were in the vascular walls but nothing definite was known. In 1915 Biedl (21) showed that the vessels in the interstitial tissue are accompanied by nerve fibers which they enclose in their walls. These sometimes penetrate between the epithelial cells. Later it was shown that the parathyroids are innervated by the sympathetic nervous system below the superior cervical ganglia. Stimulation leads to the secretion of a hormone which has the function, claimed Biedl, of acting on the sympathetic system which in turn raises the serum calcium. Thus indirectly, the hormone maintains a constant level of blood calcium.

At the present time it seems that there is only a scanty innervation, vasomotor in character. The nerves which enter the gland arterially are non-medullated and their fibers form a thin perivascular plexus about the branches. For a long time the arterial fibers escaped attention.

The nerves of the thyroid gland furnish the original supply. Ultimately the parathyroid fibers terminate within the interior of the glandular epithelium. Marine (137) questioned this point, saying that the exact method of termination is unknown. His studies were careful and extensive. He admitted the vasomotor character of the nerves.

Bandler (7) stated that he found the innervation of the parathyroids scanty in comparison with that of the thyroid but agrees that the fibers end on and between the gland cells.

We can feel certain from existing evidence that there is little or no influence exerted on the parathyroids by the central nervous system. The parathyroid nerves probably originate in the sympathetic system but it is still debatable how they influence the secretion of the gland. (Scharpey-Schafer, 175). Cannon (40) believes that the innervation exerts an influence directly on parathyroid tissue causing secretion to be released. By a variation of activity, the secretion brings about a coordination of naturally antagonistic agencies. Goormaghtigh and Heymans (81) in 1931 denervated the carotid sinus and noted postmortem hypertrophy of the parathyroids. The hyperplasia, they felt, was a reaction against vascular changes resulting from denervation and dearth of calcium. Their interpretation is questionable if made solely on the internal evidence of their paper.

Even if the gland is little affected by nerve impulses, its secretion has a definite effect on nerve tissue. Neuromuscular activity is closely tied up with the action of the parathyroid hormone by reason of the latter's regulatory function in the metabolism of calcium. The calcium ion is the chief inhibitor of skeletal muscular activity and all salts or substances which tend to precipitate calcium increase the irritability of the muscles. Without the parathyroids, skeletal muscle

would be in a state of constant contraction.

It is Cobb's hypothesis (45) that following parathyroidectomy calcium is lost from the nerve cells and hyperirritability follows. In some respects the parathyroid hormone acts like the active principle of the thymus. Both secretions are supposedly antagonistic to that of the thyroid gland. Falta's experiment (75) amplifies the evidence for a nervous control of the parathyroid glands. He performed a partial parathyroidectomy and subsequently induced tetany by cutting the gross nerves to the remaining glands. Such results may be due to an artefact since if we accept the work of Biedl (21) we should expect adequate nerve impulses to reach the gland through the perivascular fibers whose source is not in the gross nerves.

The hyperexcitability of the nerves during tetany can best be considered later with that syndrome. We might note here changes in the cells of the central nervous system which reflect the deranged condition of the nerves of the gland itself. There is a cell shrinkage with hyperchromatosis. The stainable material of the cytoplasm gradually disappears. The nucleus may be swollen or clouded but there is no complete degeneration of the nerve cells. Dye (69) in 1926 declared that the degree of cell change depended on the degree of tetany. He noted a consistent migration of the cell nucleus to the periphery.

Tetany may appear sooner in grey rats than in albinos subjected to the same treatment after parathyroidectomy. The reaction may be due to an existing

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hyperexcitability in the former group before operation. The tonic spasms of tetany depend upon a cerebellar arc and while the hypertonus is uninfluenced by decerebration, section below the cerebellum abolishes contraction. Marked cerebellar symptoms are seen in severe cases of tetany in man. The statements of Curschmann (59) relative to the cerebellar mechanism which is active during tetany confounds Bandler (7) who says the instability of the nervous system in tetany is expressed through reflex spinal arcs.

It has been stated (Barker, 9) that there is an antagonism between the suprarenal glands and the parathyroids. If present it is probably produced through the nervous system.

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The Microscopic Structure of the Parathyroids

In the parathyroids of man and mammals, three types of histologic structure can be distinguished, namely, (a) that characterized by a compact cell mass, (b) that in which retiform tissue is prominent and (c) that where lobular conformation can be observed. Welsh (210) classified them in that manner. Vincent (201) found all three types appearing in different areas of the same gland.

The extracellular protoplasm is fairly homogeneous. It is vacuolated and does not stain well with eosin. The nuclei are spherical, about four micra in diameter and show a chromatic and sometimes granular network. The cells can be divided into two classes, distinct even at low magnifications. The first type, the chief cells, (so-called "Hauptzellen") are polygonal with clear cytoplasm. They are enclosed by a distinct cell membrane. The nuclei stain faintly. The second type are called oxyphilic cells and are fewer in number. Their cytoplasm stains well with eosin but the nuclei stain better with haematoxylin. These latter cells, sometimes called eosinophilic or acidophilic, do not appear in man until ten years of age and may represent degenerative changes. At that age the need for calcium is less than earlier in life and the burden on the parathyroids consequently lessened. The exact function of each type of cell is unknown.

THE HISTORY OF THE UNITED STATES

The following are the names of the authors of the various volumes of this work:

Volume I. The Discovery and Settlement of the United States, 1492-1600.

Volume II. The Growth of the Colonies, 1600-1700.

Volume III. The American Revolution, 1700-1789.

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Volume XXIV. The United States and the Global Climate Change, 2000-Present.

Volume XXV. The United States and the Future, 2000-Present.

When DuFano's cobalt and silver nitrate method of preparation is utilized, the Golgi apparatus can be seen. A variation in position is frequent and it may be assumed that the cells are not definitely "polarized for secretion in any one direction" (Vincent, 201).

A delicate network of fine fibers surrounds the cells of the center of the gland and is different from ordinary connective tissue. The reticle it forms stains well with eosin. The cells lying near the periphery of the gland lack such a sheath. The arrangement of the cells as a group appears like palisade rows. They are radially or run in right angles to the direction of the septa of connective tissue. Collip (50) in the Harvey Lecture of 1927 cited the columnar arrangement of the cells and spoke of their separation by bands of connective tissue which are continuous with the capsule. The bands enfold the intervening capillaries as well as the fat and muscle cells.

The foetal thyroid resembles the parathyroid but soon after birth infiltration of the thyroid with fat and colloid material disperses the resemblance. The increase in the number of fat cells with age alters the appearance of the young parathyroid in man. There is little other change. Intracellular fat globules are numerous in the parathyroid of the rabbit and they are not affected by nutrition. Colloid material has been reported in the human gland in vesicles and agglomerations near the margins but it never seen intracellularly. Colloid material is more abundant in the parathyroids of lower mammals than in man,

Vincent (201) believes that the vesicles of the parathyroids increase in number when the thyroid is excised but hypertrophy is probably due to the removal of an antagonistic organ rather than because the remaining tissue assumes the function of the gland which has been removed. Similar hypertrophy is unknown in any other endocrine. Thymus nodules and cells may be seen in the parathyroid and vice versa but their occurrence can be ascribed to their intimately related anlagen.

When marked reticuliform structures are present in the parathyroids, a new type of cell is seen in the interstices which form the reticle. It is stellate in shape and has cytoplasm which is homogeneous with occasional basophilic or acidophilic granules. Such cells take up carmine or trypan blue after vital injection. The mesh-enclosed parenchyma is unchanged except when it appears to be a single coherent mass of cells crossed by a network of capillaries without the proliferation of connective tissue commonly seen.

Glycogen can be seen in the parathyroid at all ages and together with fat is thought by Jordan and Ferguson (118) to be a secretory product. Gley (80) reported that he found iodine in the gland but in lower concentration than in the thyroid. Scharpey-Schafer and Berkeley and Beebe questioned its occurrence, feeling that the iodine was in different chemical combination than the iodine of the thyroid or that the tissue analyzed was not obtained free from thyroid material.

Enlargement of the parathyroids which occurs when the calcium intake is reduced is due to hyperplasia instead of to hypertrophy of the cells. The hyperplastic effect is cumulative and increases with the length of time during which calcium is diminished in the diet. There are no accompanying changes in the thyroid (Luce, 128). Little or no regenerative ability is shown by parathyroid tissue like that seen under certain conditions in the thyroid and thymus glands. The hypertrophic effect seen after partial parathyroidectomy must not be confused with regeneration. Toland (194) expects hyperplasia when one or more of the glands fail to function. In his experimental animals he found the hyperplastic tissue to be malignant at autopsy.

Ochsner and Thompson (153), writing prior to the discovery of the hormone, were convinced of the secretory character of the parathyroid because of the continuity of cells and blood stream and the absence of a duct. They cited Peterson who had demonstrated earlier the regularity with which erythrocytes show an increased affinity for eosin in congested organs. In this the red cells resemble the cytoplasm of functioning parathyroid cells.

The histological appearance of the parathyroid of animals is essentially the same as seen in man. More commonly in the lower species the cells are arranged around a colloid-filled lumen. In birds this appearance is more common than the formation of follicles or vesicles but the avian parathyroid is less active than that of mammals. The dog parathyroid is like that of man and the

compact, lobular and retiform types of gland are seen. Sheep and goat glands are histologically identical but the clear cells of man's parathyroid are never encountered in the herbivora.

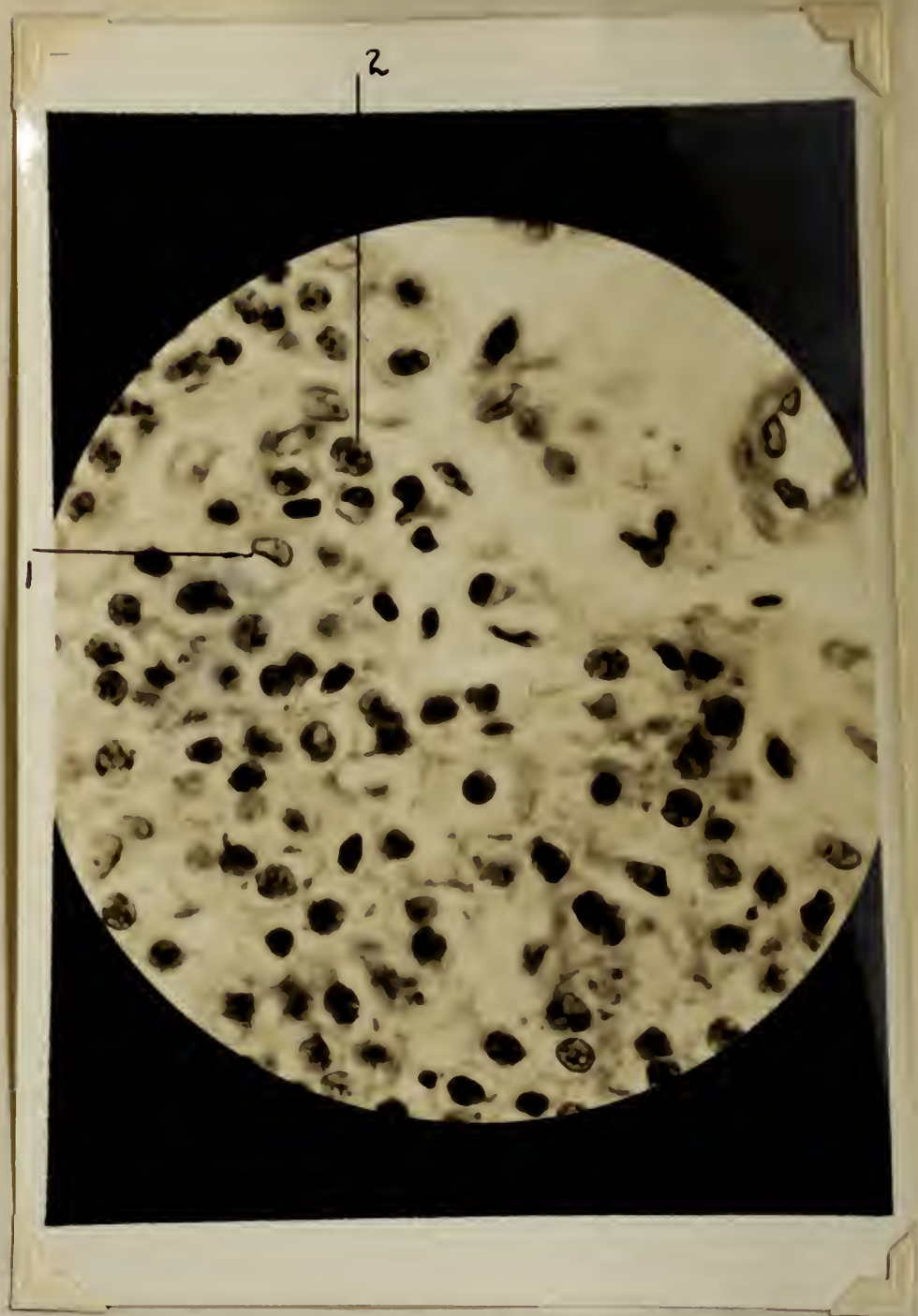


Figure Five Microphotograph of normal parathyroid
tissue (human) - 100 diameters

1. Chief cell
2. Oxyphilic cell

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The Comparative Anatomy of the Parathyroids

All the vertebrates except fish possess structures of the nature of the parathyroid glands. There is a definite relation between the thymus, the thyroid and the parathyroid glands in all animals possessing them and it is probably due to their community of origin. In the herbivora, especially the sheep and goats, the glands are so widely separated that only one pair of parathyroids can be removed inadvertently when thyroidectomy is performed. Enough parathyroid tissue/r emains to maintain life and protect against tetany. If tetany does appear, it is less severe than in the carnivora, where all the parathyroids will be removed during thyroidectomy if special care is not observed to prevent. The rarity of tetany in the herbivora and its severity in the carnivora bears no relation to the diet of each group.

The size of the gland is not a correlate of the size of the animal from which obtained. The parathyroids of the ox are smaller than those of some rabbits, whose body size is much less.

In fish no structures have been found corresponding to the glands ~~nor~~ have there been described any organs which ~~assume~~ the function of the parathyroids, at least in the elasmobranchs. It may be that the medium in which fish live has sufficient calcium in a form which can be absorbed directly through|the skin, thus obviating the necessity for parathyroid glands.

THE HISTORY OF THE UNITED STATES

The history of the United States is a story of the growth of a nation from a collection of small colonies to a great republic. It is a story of the struggles of the people to secure their rights and liberties, and of the efforts of the government to maintain the union and promote the welfare of the whole. The story begins with the first settlers, who came to the New World in search of a better life. They found a land of freedom and opportunity, and they began to build a new society. The story continues through the years of colonial struggle, the American Revolution, and the formation of the new government. It tells of the growth of the nation, the expansion of territory, and the development of industry and commerce. It also tells of the challenges the nation has faced, from the Civil War to the present day. The story is a testament to the power of the American people and the ideals of freedom and democracy.

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The anura are the lowest group in which the glands are found. This is an interesting observation since taxonomically the frogs are between the fish which have no parathyroids and the higher vertebrates in which they are always found. The glands of the anura develop in the larval stage and may be related to the change of environmental medium which requires a new mode of respiration. It is conceivable, since there is a structural relation between the development of the respiratory and branchial pouch organs, that in this group at least, there may be a functional relation, as well. Waggener (205) has shown that the marked powers of regeneration possessed by the anura do not hold for the parathyroids. The glands are discrete and can be easily removed. After parathyroidectomy, the anura show typical symptoms of underfunction^{but} tending to become normal when hormone treatment is instituted.

The occurrence of parathyroid glands has been reported in turtles. They are found at either side of the thymus at the base of the neck. Apparently they contain large amounts of lipoid for their color is a fatty yellow.

All the the thyroid tissue of birds is in the cavity of the thorax. One or two parathyroid glands can be distinguished at the upper or lower poles of the gland. Marine (138) found hypertrophy and hyperplasia of the parathyroids of fowls following thyroidectomy without compensatory enlargement of other organs. Birds

who were given calcium either parenterally or by mouth showed less overgrowth of the glands than did those whose calcium intake was restricted.

Marine concluded that the calcium protected against hypertrophy and that the avian parathyroid gland and hypertrophic was more susceptible to hyperplastic changes than that of most mammals.

In rodents, projection of the parathyroids from the surface of the thyroid gland is not uncommon. One parathyroid glandule per side is the rule in this group. In the field mouse, there is a free parathyroid at the upper and lower edge of the thyroid gland. Occasionally there are accessories scattered through the thyroid and at the tip of the thymus. They may be in the thyroid or on its surface below the pole. As many as eleven accessory glandules have been reported in the rat. Vincent and Jolly (201) found that parathyroidectomy did not always lead to fatal results in rats and guinea pigs. The reason was probably due to anatomical difficulties because of which tissue was overlooked.

In the ruminants the position is aberrant. The glands of the sheep and goat are found nearer the cranium than in lower species, on the inner surface of the submaxillary glands, at the bifurcation of the carotid artery or somewhere along its course. The fourth glandule is located at the center of the thyroid. Shapiro and Jaffe (176) found that accessory glandules were widespread through the neck and upper thorax and in the thoracic thymus of the sheep.

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The glands of the rabbit are four in number. They are partly embedded in the medial border of the thyroid and one is found at either end of the two lobes. They can seldom be identified except in sectioned and mounted tissue. For some obscure reason rabbits do not show a uniform response following extirpation and are unsuitable for experimental use. Erdheim found as many as nine accessory glandules in the hare in addition to those normally placed in the interior of the thyroid. The accessories are often close to the carotid artery and hang from a delicate arterial peduncle.

Biedl (21) states that the glands are most constantly placed in the cat. Most frequently they are embedded in the thyroid but may be in the thymus and thoracic region. Shapiro and Jaffe (176) found accessory glands in fifty per cent of their cats but they may have mistaken other tissue for the parathyroids.

The glandules are also embedded in the thyroid in the dog. There is an external depression at the upper pole ~~of the upper pole~~ of the thyroid in which the superior pair lie. The inferior glands are embedded in the mid-thyroid. Accessories are found in sixty per cent of dogs. MacCallum (134) cites Liezenska who found the internal parathyroids to lie just under the thyroid capsule in the supportive tissue about the trachea and around the branches of the thyroid artery.

The horse has one lobulated glandule on each side. It is about 1 cm. in diameter and located in

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the peri-thyroid areolar tissue. The position varies according to the position of the thyrolaryngeal artery with which it is associated. In the ox, the glandules are at the level of the isthmus of the thyroid. The parathyroids of steers and aged cows show oxyphilic cells like those of man. None of the common laboratory animals possess these cells.

In the apes, the outer parathyroids are on the lateral surface of the thyroid gland. In *Macacus rhesus*, the external parathyroids are at or about the mid-lateral surface of the thyroid gland. The internal glands are embedded near the the inner surface and are larger than the outer pair. As many as eight accessories have been found in the monkey.

Little light as to function is shed on the parathyroid glands by a study of their comparative anatomy. Variations are more frequent in lower than in higher animals. It is invariable to note tetany following the removal of the parathyroids.

The Pathological Changes Affecting the Parathyroid Glands

Although most of the research relating to the parathyroid glands has been of the experimental type, much physiological knowledge has been acquired from observations of a negative nature, that is, of the appearance of the gland in diseased conditions. There is little gross change but some of the microscopic changes are definitely abnormal. Sandstrom noted large areas where there were no cells and referred to them as spaces of cystic degeneration. He did not recognize their relation to glandular pathology. Sandstrom also described amyloid infiltration but the condition may be entirely normal and related to glycogen formation. The latter process is found without any functional abnormality. Fatty material in abundance is often seen and it may be the cause of atrophy of the parenchymatous cells (Ochsner and Thompson, 153).

There is little early pathology in experimental tetany. In many of the syndromes with tetanic symptoms, attempts to find histologic pathology have been unavailing. In tetanus, infiltration of mononuclear cells was found in two cases but other changes were limited to an increase of colloid (Ochsner and Thompson, 153).

Hemorrhage into the glands is common in the tetany of children but the parathyroids undergo no further change. There is no morphological confirmation of Erdheim's belief that rachitis is caused by hypoplasia of the glands. In certain of the osteologic complexes, hyperplasia is almost always found.

The yellow color of the adult parathyroid is due to the fat which it contains. The xanthochromic appearance is a macroscopic aid in differentiating lymphoid tissue, accessory thyroid nodules and sympathetic nerve ganglia from the parathyroids. In general the fatty infiltration increases with age but is not necessarily an accompaniment of age. Increase in fat is better associated with lipoid disorders of metabolism than with parathyroid disease.

When colloid is present it is widely distributed. It should be considered per se to be abnormal nor is there an anomaly in the complete absence. Circumscribed areas of colloid cause the parathyroid to simulate the appearance of the thyroid gland. Continued secretion of the colloid material pushes back and flattens the cells so that the follicle appears and increases the resemblance.

Degenerative changes appear in the parenchyma but cloudy swellings and acute degenerations due to postmortem changes must be ruled out in tabulating the occurrence due to parathyroid disease. Oedema of the parathyroids may cause enlargement, softening and pallor. In this gland it is a sequella or correlate of general oedema of the neck organs. Whether the fluid is intracellular or extracellular can be demonstrated microscopically. It is one of the few lesions of tetany.

The stroma or septa of connective tissue may increase to the point where fibrosis is the dominant character of the organ. Then the gland is broken up into islets. Such a condition has been described as "chronic interstitial parathyroiditis" and "parathyroiditis chronica fibrosa". Almost without exception the inflammation is found in poorly nourished individuals, those with heart disease, cirrhosis of the liver or chronic tuberculosis.

The parathyroid is remarkably free from invasion by infectious agents. The exception is the attack of the tubercle bacillus in acute miliary tuberculosis. The caseous appearance which results is typical of that organism's ravages.

The tumors of the parathyroid should properly be considered with the conditions they cause. The first parathyroid neoplasm was described by deSanti in 1900. Before that time they were thought to be foetal adenomas of the thyroid gland. DeSanti's tumor was found in the carotid region and was a large vascular growth whose structure corresponded to parathyroid tissue. The majority of tumors are adenomata and rarely are malignant. They are small nodules occupying all or part of the gland. It may be that their incidence is higher than is known and would be found more often if search were made at autopsy. Such an examination is not made if there has been no suggestive clinical pathology. The line of demarcation between hyperplasia and adenomata of the parathyroids is not at all clear cut. Hyperplasia represents a response to a functional need rather than a neoplastic effort.

Adenomata of the parathyroids are frequently an accompaniment of ^a thyroid adenoma and may represent a metastasis. Sometimes a thyroid adenoma is found on section to have arisen from the parathyroids. The true parathyroid adenoma is a distinct, encapsulated nodule of yellow-brown and its cavity is filled with an amber fluid. Later it will be seen that neoplasms of the parathyroid found in the fibrous capsule are very common in osteitis fibrosa cystica or von Recklinghausen's disease. However, such tumors originate in the parathyroid. Neoplasms might be expected to metastasize into the gland from adjacent tissue because of the marked vascularity of the parathyroids. When this happens, the metastasis originates in a carcinoma of the breast or a lymphosarcoma of the mediastinum.

The Normal Metabolism of Calcium

Not less important than the fat, carbohydrates and protein which form the basis of an adequate diet is the calcium without which proper skeletal growth can not take place. The bone which forms the supporting structures of vertebrates is largely composed of tri-calcium phosphate. Because of the rapid growth of children, their need for calcium in the diet is great. One gram of calcium per day is the maintenance level up to adolescence. After that one half gram suffices. The quantities needed can be obtained respectively from one quart and one pint of milk. Fruit and vegetables augment milk as a source of calcium.

Lime or calcium, besides being segregated in the bones, is present in considerable amounts in the blood and vital fluids. Some part of the circulating calcium is ionizable and can diffuse through cellular and tissue membranes. The balance of the circulating calcium is tied up in organic, non-ionizable combinations. Cantarow (41) found the average spinal fluid calcium to be fifty per cent of that in the blood and approximately equal to the diffusible calcium fraction of the blood. Variations in calcium content of spinal fluid may be due to ^achange in the serum calcium level or to changes in the permeability of the cell membranes between the blood and subarachnoid system, the choroid plexus.

Variation in the blood calcium beyond small limits is dangerous. If the variation is toward lower levels, there follows hyperexcitability of the nerves and muscles in proportion to the decrease. Calcium loss depresses the stability of the ^{central} nervous system and the peripheral nerves. Convulsions may occur if the drop be sufficient. Intravenous administration of sodium citrate diminishes the blood calcium because two sodium ions replace a calcium ion and the latter is eliminated in the feces or urine as calcium phosphate.

Cannon (40) has a theory of homeostasis ^{which} supports the belief that the parathyroids have a stabilizing effect in calcium metabolism. The normal concentration of blood calcium is about ten milligrams per hundred cubic centimeters of blood serum. The cells contain about 0.3 milligrams per hundred cubic centimeters. When the blood level drops to five milligrams, tetany supervenes.

Hypercalcemia or increase in blood calcium has equivalent dangers. The condition brings on languor and diminished muscular and nervous sensitivity as well as gross alterations in the consistency of the blood. Any condition which causes an increase of serum calcium in man above the normal level causes also a retention of non-protein nitrogen and urea indicating involvement of the kidneys. The blood phosphorus may rise at the same time to twice its normal level.

The osmotic pressure may rise and the blood become too viscous to circulate. Intravenous calcium chloride and acid sodium phosphate given together raise the blood calcium and bring on the typical symptoms of hypercalcemia. The calcium in an acid medium seems to produce the effect for the acid sodium phosphate when given alone produces no change.

During pregnancy, lactation and oestrus in animals and during menstruation in women, the need for calcium is increased. If it is not supplied, tetany appears. However before the spasms begin, there is decalcification of the bones and teeth. It will be seen later that calcium bears a distinct and peculiar relation to rickets and the lack of Vitamin D.

Administration of calcium to thyroparathyroidectomized animals leads to a deposition of calcium in their bones (as tricalcium phosphate) and if continued for a long time there is body equilibration of calcium especially when parathyroid extract is given. The retention of calcium is increased by the exposure of animals to sunlight or by the ingestion of cod liver oil and Vitamin D. If the calcium intake is low in proportion to the phosphorus intake, there is an abnormal irritability apart from serious symptoms.

The normal calcium of plasma may be maintained at a constant level and in equilibrium between inorganic and organic calcium by a compound resembling calcium citrate but not identical with it. The formation of the compound

The number of cases was 100 in 1900, 150 in 1901, 200 in 1902, 250 in 1903, 300 in 1904, 350 in 1905, 400 in 1906, 450 in 1907, 500 in 1908, 550 in 1909, 600 in 1910, 650 in 1911, 700 in 1912, 750 in 1913, 800 in 1914, 850 in 1915, 900 in 1916, 950 in 1917, 1000 in 1918, 1050 in 1919, 1100 in 1920, 1150 in 1921, 1200 in 1922, 1250 in 1923, 1300 in 1924, 1350 in 1925, 1400 in 1926, 1450 in 1927, 1500 in 1928, 1550 in 1929, 1600 in 1930, 1650 in 1931, 1700 in 1932, 1750 in 1933, 1800 in 1934, 1850 in 1935, 1900 in 1936, 1950 in 1937, 2000 in 1938, 2050 in 1939, 2100 in 1940, 2150 in 1941, 2200 in 1942, 2250 in 1943, 2300 in 1944, 2350 in 1945, 2400 in 1946, 2450 in 1947, 2500 in 1948, 2550 in 1949, 2600 in 1950, 2650 in 1951, 2700 in 1952, 2750 in 1953, 2800 in 1954, 2850 in 1955, 2900 in 1956, 2950 in 1957, 3000 in 1958, 3050 in 1959, 3100 in 1960, 3150 in 1961, 3200 in 1962, 3250 in 1963, 3300 in 1964, 3350 in 1965, 3400 in 1966, 3450 in 1967, 3500 in 1968, 3550 in 1969, 3600 in 1970, 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depends upon the supply of parathyroid hormone. (Bodansky, 26) Greenberg and Greenberg (84) deny the presence of a compound of that nature in the blood. Their evidence appears quite valid.

The total calcium of the body of a one hundred and fifty pound individual amounts to 3.8 pounds or to 2.5 per cent. Much of the calcium excreted by the body goes through the portal circulation and the bile to the intestine.

Calcium is very necessary to the clotting of blood. It forms an important part of the clot. When calcium is low the clotting and bleeding times are increased. Calcium also participates in various body enzymatic processes. It is intimately tied up with body phosphorus and changes in the concentration of one substance are paralleled by changes in the other. During starvation, the bones are called upon for calcium and phosphorus and the excretion of both is increased. Strangely enough, calcium is lost from the body during hypoparathyroidism and hyperparathyroidism. In the former it is due to faulty absorption and in the latter to increased mobilization of deposit calcium.

At the expense of relaxation, calcium favors a contracted condition. (Parsons, 156) Sidney Ringer, an English physiologist, demonstrated about 1880 that calcium in normal saline when perfused through an isolated heart maintained the beat when the normal saline alone failed to do so. The antagonism between calcium and potassium were shown in the same manner by Jacques Loeb who used nerve-muscle preparations. If calcium preponderated, there was a tendency to relaxation

but if potassium preponderated there was a tendency to contraction. If the two ions were in equilibrium, the muscle was in normal condition.

For the proper absorption of calcium, a certain amount of fat is needed. (Holt and Howland, 1907) Absorption proceeds best when the ratio of calcium to fat in the diet is one to twenty. This is the approximate ratio of the two as found in cow's milk.

It can readily be seen that the role of calcium in the body economy is not simple. The effects of deranged calcium metabolism extend to every cell and tissue. It is not strange that a glandular homeostat is needed.

Factors Which Assist in the Absorption of Calcium

It has been shown that those factors which aid in calcium absorption are favorable to the parathyroids and their lack antagonistic. Sunlight is a typical example. In winter when the actinic rays are decreased in number, the parathyroids are found to be larger than in summer when the actinic rays are more plentiful. (Larson, 124) Nonidez and Goodale (152) in 1927 studied the histology of the chick parathyroids deprived of ultraviolet light. All the rays permitted to reach the chicks (white leghorns) were below 312 uu in wave length. Their diet was poor in antirachitic Vitamin D. After death the glands were fixed in Botin's fluid, sectioned and stained with haematoxylin and eosin. A marked degree of hypertrophy and hyperplasia was seen probably due to an effort to compensate for the scanty ultraviolet rays. Glands obtained from the same group of chicks at other stages of treatment showed regression and degeneration. Much keratin and mucoid material were present. The cells had decreased in size and lacked the accumulation of secretion seen in the normal chick parathyroid. (cf. also Higgins, Foster and Sheard, 101)

Biedl (21) affirms that sunlight increases the hypercalcemic effect of parathormone. He recommends a combination of sunlight, cod liver oil and diet as prophylaxis against tetany. Biedl cites the infrequent occurrence of the condition in breast fed infants. The implication is that their calcium intake is higher than that of children fed on artificial formulae.

MacLeod (135) is of the opinion that parathyroid activity is depressed in children who suffer a deficiency of Vitamin D or sunlight. The wave length of the ultra-violet rays in sunlight is between 300 and 297 uu. Rays which fall outside these limits are ineffective in stimulating the absorption of calcium. The studies of Hess are cited by MacLeod to demonstrate that Vitamin D and sunlight act upon skin cholesterol which when irradiated affects the blood calcium level in the same manner as irradiation of the whole body.

Irradiation before parathyroidectomy leads to hypertrophy of the glands but is not accompanied by a rise in blood phosphorus. There is a smaller drop in blood calcium and a quicker recovery from the acute stages of tetany than is seen in animals who have not been irradiated before operation. Irradiation of rabbits has the same effect whether they are normal or lack the parathyroid glands. Swingle and Rhingold (185) showed that radiated dogs develop tetany as quickly as do non-radiated dogs but irradiation after operation prolongs life and lessens the severity of the attack. The animals eventually die of exhaustion regardless of the treatment. The increased absorption and retention of calcium because of the ultra-violet treatment is insufficient to avert the fatal outcome. Jung (116) corroborated the work of Swingle and Rhingold.

Vioosterol did not protect guinea pigs from the demineralising effects of experimental hyperparathyroidism. Brpugher (31,32) claimed that 0.4 cc. of acterol per day with milk from the time of operation prevented tetany.

If the milk was vomited, then tetany ensued. The recovery was quicker if cod liver oil was given and speeded further when pure Vitamin D was administered. Whether this plan of therapy increased the absorption of calcium or stimulated hypertrophy is uncertain. Some writers claim that the action of Vitamin D and parathormone is identical. The action of the secretion of the glands is more potent since life can be maintained longer on a D-free existence than on a parathyroid free regime.

It may be that the cod liver oil given to parathyroid-ectomised dogs not only improves calcium absorption but also mobilizes it and changes non-ionized calcium to an ionized form. Greenwald and Gross (91,92) disclaim the good effect of cod liver oil and choose to accept the idea ~~the idea~~ of protection from tetany by accessory tissue and hypertrophy. They admit that cod liver oil stimulates parathyroid activity and that the effect of parathormone is enhanced when it is given at the same time. The cod liver oil varies in effect depending on the potency of the parathyroid extract given, the age and diet of the subject and the need for calcium at the time of administration.

Pappenheimer (155) agrees that cod liver oil and viosterol in therapeutic doses are antirachitic when neither the parathyroids or the thymus gland are present. Reed and Seed (166) make similar observations. Morgan and Garrison (147) observed that Vitamin D-free dogs respond well to parathormone and never display the symptoms of overdosage. Jones (115) gave 20 cc. cod liver oil pre-operatively and declared that he prevented tetany

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by that means. When given only post-operatively, cod liver oil was ineffective. Luce (128) saw hyperplasia of the parathyroids in normal young rats after being fed a Vitamin A deficient diet. Rose and Stucky (169) found parathyroidectomy to be invariably fatal in Vitamin B deficient rats.

The Physiology of the Parathyroid Glands

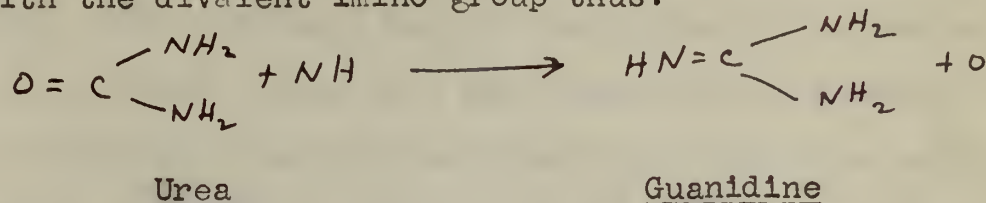
From among the theories which have been postulated to explain the function of the parathyroid glands, only two have been backed by a weight of experimental evidence. Of these, there are so many discrepancies in the "toxin" theory that we may pass over it with little credence. Following the isolation of parathormone by Collip in 1925 and his subsequent publications concerning its effect on normal and parathyroidectomized animals, little question remained as to the authoritativeness of the theory of a calcium regulating function of the parathyroid glands.

In 1909 Berkeley and Beebe thought the symptoms of tetany were due to a deranged metabolic process which permitted the accumulation of a toxic substance within the body. At that time the subject was too little understood to be discussed at great length. In 1912 Koch found an excess of methyl guanidine in the urine of dogs (6 - 16 mgs. per 100 cc.) when the parathyroid glands were removed. Recalling the theory of Berkeley and Beebe, Paton and Findlay(158) and their Glasgow colleagues began work in 1916 along that line. They published statements to the effect that intravenous injections of guanidine caused tetany in rats. They claimed further that the purpose of the parathyroids was to detoxify these substances and to break them down to their normal end products, creatine and creatinine. Later Paton and Findlay published a series of papers to show the relation of tetany to guanidine intoxication.

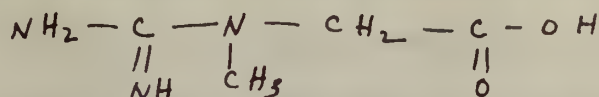
Such statements might seem reasonable if it could be shown that guanidine and its addition products existed normally in appreciable amounts in the body. Paton and Findlay at first believed that guanidine was responsible for muscle tone and that the parathyroids regulated the muscles indirectly by their effect on guanidine metabolism. The parathyroid secretion, if one were present, was thought to be like the complement of Ehrlich, linking guanidine to the protoplasm of cells within which protein metabolism was effected. An activity of such proportions could not take place in a structure as small as the parathyroids.

Paton and Findlay further thought that an injection of guanidine at intervals should produce a picturesque histological appearance of the parathyroid gland at rest, in various stages of activity and even in a state of functional strain. Adult rabbits when injected intravenously with five per cent guanidine nitrate in normal saline solution showed a marked depletion of fat globules of the gland within eighteen hours. Other animals whose glands were examined after forty eight hours were entirely normal. If the injections were repeated long enough and often enough to give hypertonicity to the muscles there was brought about hypertrophy, hyperplasia and an increase of acidophilic cells. There was also a permanent decrease in the number of fat globules. Therefore, reasoned Paton and Findlay, guanidine was involved in the etiology of parathyroid dysfunction.

Guanidine, or deacetylated creatine, is an interesting substance in that it can be formed in vitro by replacing the divalent oxygen group in the urea molecule with the divalent imino group thus:



If the metabolic processes proceed further, it is found that creatine or methyl guanidine acetic acid, ($\text{C}_4\text{H}_9\text{N}_3\text{O}_2$) is formed. Its anhydride is creatinine:



Creatine is not stable and can be determined only as the anhydride. If creatine is boiled with mercurous oxide, it reduces the latter and is itself oxidized to methyl guanidine and oxalic acid.

Vincent (201) believed that other toxins which are disintegrative products of body metabolism may contribute to the production of tetany. Among them he listed ammonia, xanthin, histamine and thymus secretion. Kendall, who later isolated thyroxin, believed that the body when deprived of parathyroid secretion failed to convert ammonium carbonate to urea but stopped at the guanidine stage. The toxins which result produce irritation of the central nervous system and cause the symptom-complex of tetany.

McCarrison (143) stated that the symptoms of tetany were caused by the toxins elaborated by the fecal anaerobes whose growth is normally inhibited by the parathyroids. He classified the toxins of fecal origin concerned in parathyroid pathology as a) those resulting from impaired

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metabolism and b) those resulting from bacterial action in the bowel.

McCarrison (143) further stated that parathyroidectomized animals thrived better on vegetables than on a meat diet. The inference is that the putrefactive bacteria are nourished better by the decomposition products of the protein. The true explanation is that the animals used in his studies (goats) to whom a herbivorous diet is natural have a parathyroid gland so formed that complete extirpation is almost impossible and bits of active and aberrant tissue are left. McCarrison advanced further proof of his thesis by experiments in which the transfusion of normal blood supposedly diluted the toxins and resulted in the abolition of tetanic symptoms. The conception of an internal secretion with an antitoxic function was popular in 1917.

There is little doubt that guanidine causes ^{some} symptoms identical with those of parathyroid tetany but it can not be said that all types of tetany are due to guanidine poisoning. Obviously guanidine produces tetany in dogs and raises the electrical and mechanical excitability of nerves and muscles. Frog muscle bathed in guanidine acts like a similar preparation bathed in the serum of a parathyroidectomized dog.

Dragstedt, (Südan and Phillips (68) in 1923 advanced evidence that seemed in harmony with the concept of the parathyroids as a detoxifying mechanism. They kept parathyroidectomized animals alive indefinitely on a carbohydrate diet of white bread, lactose and milk presumably thereby reducing the protein decomposition products to a minimum.

Greenwald (86) in 1924 was unable to demonstrate a toxin in parathyroid tetany. He found only two chemical changes, namely, a) a lowered calcium of serum and b) a diminished excretion of phosphate by the kidney. On the basis of his findings he refused to accept the toxin theory. Collip and Clark (54) in 1926 tested the guanidine intoxication theory by studying the non-protein nitrogen and urea curves in untreated parathyroidectomized dogs. He compared his findings with those found after the injection of guanidine and in no case was the curve parallel. The findings suggested that ^{guanidine}urea is converted into urea because of the increase of the excretion of the latter and this they felt was due to the diuretic action of guanidine on the kidney. Of this there is no conclusive proof. Collip and Clark noted no change in the blood calcium when guanidine was administered.

Parathyroidectomized dogs receiving adequate calcium by mouth had a normal concentration of calcium in the serum but when the intake was diminished the serum calcium dropped and tetany disappeared. Collip and Clark (54) first mentioned the possibility of plasma calcium being maintained at a level by a substance resembling calcium citrate but not identical with it and for whose formation parathormone was needed. It was this compound which Greenberg and Greenberg (84) in 1932 disclaimed.

Vines (202) was convinced of the influence ~~of the~~ influence of the parathyroids in controlling guanidine metabolism and devised an elaborate ^{method} for determining the guanidine destroying index of the blood. He made a standard solution of guanidine acid to phenol red and after adding measured amounts of normal saline and one per cent calcium chloride estimated the guanidine as guanidine picrate. A quantity of this solution equivalent to .065 gram of guanidine was added to the serum to be tested and the mixture incubated at 37° C. for four days under constant aeration. The guanidine was again determined and the difference between the two determinations expressed as Vines' index of guanidine-destroying activity.

Luckhardt and Rosenbloom (130) treated guanidine poisoning and tetany by intensive diuresis proceeding on the theory that the water soluble toxins would be eliminated by the kidney. (Guanidine is very soluble in water and alcohol)

The points of differential diagnosis between parathyroid tetany and that of guanidine poisoning are meagre but sufficient to distinguish the two. In the latter there is fatty degeneration of the liver with accompanying symptoms but no general congestion and hyperemia of the viscera as in parathyroid tetany. There is necrosis of the abdominal organs in both conditions. Elkourie and Larson (71) state that the symptomatology is very different. Collip and Clark (54) found that guanidine produces a continued rise of blood urea nitrogen and non-protein nitrogen soon after the onset of convulsions. In parathyroid tetany the animal is moribund before a similar rise is seen.

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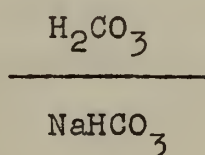
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Further study was made of the effect of carbohydrate diets in the control and prevention of tetany after 1925. Salvesen (174) found milk was ineffective if the calcium contained therein was precipitated by rennet. Monkeys fed on bread and milk suffered only a transitory tetany and recovered from the nervous symptoms completely and permanently. The completeness of extirpation of the parathyroids is questionable in those animals.

Vincent (201) felt that the increased acid production following parathyroidectomy led to displacement of certain inorganic cations especially calcium from the inorganic compounds of the body. The released calcium was then eliminated as soluble salts of carbonic and phosphoric acid. MacLeod (135) felt that tetany is due to a disturbance of the acid-base balance of the blood. Tetany becomes manifest when the alkalinity of the blood and tissues rises above a pH of 7.4. The tetany of forced breathing and the correlative alkalosis which accompanies it supports such a concept. When carbon dioxide is removed from the system by hyperpnea, the numerator of the equation



is reduced and a relative alkalosis produced. The total acidity of the urine is reduced and there is a rise in the excretion of alkali in an effort to adjust the ratio. Bryan and Garrey (34) show this effect in a series of dogs where tetany was produced experimentally.

Such tetany is not quickly relieved for the excretion of the acid carbonate ion by the kidneys is less rapid than the excretion of carbon dioxide by the lungs.

The tissues aid in the reaction by their buffering action and soak up some of the excess bicarbonate from the blood. The hydrogen ion concentration of the blood drops as that of the tissues rises. MacLeod generalizes to the extent of saying that any mechanism which decreases body acidity and causes an increase of base leads to tetany. However, it has been noted by Gates and Grant (79) that there is not a total alkalosis in parathyroid tetany nor is there a diminution of calcium in alkaline tetany. Such a statement serves to exclude MacLeod from all controversy rather than to show the cause of the syndrome. He says that "the tetanic syndrome is not an entity but a manifestation of neuromuscular excitability." In the attempt to correlate extant theories he advances a hypothesis which is plausible but not chemically sound. Briefly stated it suggests that the HCO_3^- ion and the imido group of protein derivatives (guanidine, creatine, etc.) influence the union of calcium with blood colloids and body tissues and increase the bound calcium at the expense of the diffusible form. When this proceeds sufficiently tetany appears.

The Parathyroid Glands and Parathyroid Tetany

The constancy of low calcium and the beneficial effect of calcium administration during tetany leads us to feel confident that the function of the parathyroid gland is to maintain a supply of calcium in the body in order that hyperexcitable states of nerve and muscle may not develop. Such an effect can be demonstrated in vitro by the use of an isolated nerve-muscle preparation. MacCallum and Voegtlin (133) in 1909 declared that in the absence of the parathyroids a substance was formed which could combine with calcium, extract it from the tissues and cause it to be eliminated from the body. These investigators noted the occurrence of tetany following ablation of the glands (tetania parathyreopriva). They also observed the consistent diminution which accompanied it. On the basis of the findings they believed the actual function of the parathyroid secretion is to keep calcium in solution by promoting its ionization and by stimulating defective absorption of that substance. Normal absorption proceeds more rapidly than excretion of calcium by bowel and kidney. In this way the parathyroids control blood calcium levels and so influence the function of the nerve and muscle tissue of all organs.

Cannon (40) associated the glands with the regulation of the calcium metabolism since disorders of the parathyroids are associated with decalcification of dentine and defective formation of bone calluses following fractures. A low calcium diet leads to parathyroid hyperplasia without a

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fall in blood calcium. A drop of fifty per cent of the total calcium may take place before tetany occurs. The same margin prevails in hypoglycemia before symptoms comparable to insulin shock are seen.

By cross circulation experiments MacCallum and Voegtlin had shown in 1911-12 that hyperexcitability of the nervous system is peripheral and depends on some change in the blood. When blood from a tetanic animal is perfused through the leg of a normal animal, the excitability of the nerves rises to a high level and parathyroid extract has little effect in lowering it. These symptoms lead to changes in the nerve cells of the cord. The increased muscular activity results from the action of potassium ions on nerve cells which activity had previously been inhibited by the calcium ions with which they were in equilibrium. In 1913 the same workers showed by direct analysis that the calcium content of serum was low during tetany. The average figure found by Howland and Marriot (107) was 5.6 mg. per 100 cc.

MacLeod (135) cites the work of Jacques Loeb who demonstrated fibrillary twitching in an isolated muscle placed in calcium-free Ringer's solution. When the vessels of a normal animal were perfused with its own blood which had been dialyzed against a calcium-free isotonic solution, the same fibrillation could be seen. These facts, when added to ~~that of the~~ enormous increase of calcium excretion during the depression, weakness, anorexia, vomiting, diarrhea which make up the condition of tetany, make safe the conclusion that a derangement of body calcium is the principal etiological factor. In the face of such evidence those

who champion the "toxin" theory are overwhelmed and their evidence appears meagre and pregnable.

Voegtlin (203) in 1917 declared that the function of the gland was not known but agreed that a minimum amount of parathyroid tissue was necessary for the maintenance of life and normal metabolism. He understood that parathyroid insufficiency led to irritability of the nervous system and felt that it was caused by the withdrawal of soluble calcium from blood and tissues. Insufficiency of the glandular secretion led to alkalosis of a generalized nature as a result of the active tetany.

Cameron and Moorhouse (37) believed that tetany was due to a drop in an organic calcium compound following removal of the glands basing this on the fact that the blood clots well after parathyroidectomy, whereby ^{they} ~~he~~ concluded that an ^{inorganic} ~~ionic~~ calcium compound was not involved but rather an organic compound which was metabolically reduced at the same time as the hormonal supply. While tetany was present there was found to be a correlation between the degree of tetany and the concentration of the serum calcium. As the calcium content was raised, the clinical condition of the animal improved.

Crile (57) felt that elaboration of a secretion was the only function of the gland. The hormone acted ~~elsewhere~~ ^{gland} than in the ~~body~~ and controlled blood calcium. By the presence of the hormone in the circulating fluids, it could be carried to every cell which required it. Marine's

finding (138) that calcium alone would not maintain an animal deprived of all parathyroid tissue led to experiments in which only partial parathyroidectomy was done. In ~~such~~ animals where some tissue was left, calcium did maintain life and thus the vital need of active tissue was corroborated.

The coagulation time is ^{thought to be} lengthened in tetany since the calcium which activates thrombin is lacking. The proof of the idea is lacking and should be forthcoming when it is determined whether inorganic or organic ^{calcium} compounds are affected during tetanic spasms.

A consideration of the effects of varying degrees of parathyroid activity will demonstrate the function of the gland more clearly. Hypofunction and tetany were known and described long before the gland was discovered. Spasms of the glottis and extremities had been described in 1815 (see Appendix A) but little attention was given to the disease until 1830. It was not until 1896 that tetany was associated with the glands by Gley (80).

One to two days after the removal of the glands of a laboratory animal, there are symptoms of intoxication and a loss of muscular control. Tremors and stiffening of the limbs occur and in due course increase in violence. There is a rise in temperature, respiration and heart action. A drop in blood calcium is seen on analysis and in nine to ten days, a dog so affected dies in convulsions if untreated.

In man, especially in children, a similar though less intensive group of symptoms is seen. There are also accompanying gastro-intestinal manifestations. Holt and

Howland (107) describe the condition vividly and cite as the most notable symptom, arthrogryposis, a carpopedal spasm in which the hands and feet are contracted bilaterally and drawn toward the center of the body. The upper extremities are affected first but the contracture soon spreads to the feet and legs. The fingers are flexed at the metacarpal-phalangeal joints and the thumbs are adducted almost to the little finger. The wrist is flexed acutely and the hands are drawn to the ulnar side. If the spasm is extreme there is no motion possible at the wrists. The feet are extended as in equinovarus but motion at the large joints is generally free. The spasm can be controlled and voluntarily overcome at times but as soon as the active motion ceases, the former attitude is resumed. There is pain but no loss of consciousness. (See Figure Seven)

The reflexes may be increased, decreased or may be unchanged. Usually there are disturbances of balance (with forced cerebellar movements). A drop in blood sugar and liver glycogen takes place. Probably it is burned in the course of increased muscle effort. Lactic acid can be demonstrated in the urine. The pulse and heart rate are exaggerated. Salivation, vomiting and diarrhea may occur. The temperature may rise two or three degrees Centigrade. Death occurs in acute cases from cramping of the respiratory muscles and in chronic cases from emaciation. Occasionally the end comes during a convulsion.

the first thing I noticed when I stepped out of the car was the smell of the sea. It was a salty, briny scent that seemed to permeate the air. I took a deep breath and felt a sense of peace wash over me. The sun was shining brightly, and the waves were crashing against the shore. I walked along the beach, feeling the sand beneath my feet. The water was so clear, and the sky was so blue. I felt like I had found a new world. I had heard so much about the beauty of the ocean, but I had never experienced it before. Now, I was here, and I was in awe. I had found a place where I could escape the stresses of life and just be. I had found a place where I could be happy. I had found a place where I could be me.

The first thing I noticed when I stepped out of the car was the smell of the sea. It was a salty, briny scent that seemed to permeate the air. I took a deep breath and felt a sense of peace wash over me. The sun was shining brightly, and the waves were crashing against the shore. I walked along the beach, feeling the sand beneath my feet. The water was so clear, and the sky was so blue. I felt like I had found a new world. I had heard so much about the beauty of the ocean, but I had never experienced it before. Now, I was here, and I was in awe. I had found a place where I could escape the stresses of life and just be. I had found a place where I could be happy. I had found a place where I could be me.

Paton, Findlay and Watson (158) do not believe the clonic spasms or reflex movements alternating between contraction and relaxation depend on the cerebrum or cerebellum since they persist after ablation of those parts of the brain. Suppression of their function by amaesthesia causes an increase of clonus, but the clonus disappears after destruction of the anterior roots of the spinal cord. Evidently the seat of origin of clonus is not in the peripheral nerves or the muscles. Biedl (21) observed the hind limbs of his dogs undergo sudden contractions while the upper part of the cord and connecting limbs were in a tonic condition due to the effect of the tonus on the labyrinth and cerebellum. Biedl cited Horsley and Lenz who found that on removal of one half the cerebral cortex the tetanic condition continued on the contralateral side.

The lower neurones are principally affected during tetany. The nerve endings of the motor nerves are first affected followed by an involvement of the muscle fibers and of the sensory nerves. The ablation of the cerebral cortex seems to intensify the symptoms because of the removal of inhibitory influences. When the cortical ablation is unilateral the symptoms are increased on the opposite side but when parts of the cerebellum are removed the increase of symptoms is seen on the same side. Section of the mid-cord in a tetanic animal does not stop the jerking but the rhythm is changed. The tonic contractions then cease below the section but the twitchings proceed above it. Section of the dorsal roots does not affect the tremors but section of the motor nerves abolishes

them.

Tetany may last for several hours or for days if untreated. The muscular contractions may be continuous or there may be only a single attack which is acute. The larynx or glottis and tongue may be involved and laryngismus stridulus is heard instead of the normal tones of speaking or crying. The "crow" of tetany is heard in children at every inspiration. Holt and Howland (107) associate tetany with a negative calcium balance as well as with lowered blood calcium. They also claim that tetany may be familial and that the glands may be entirely normal when tetany is seen. Such a statement is properly applicable only to the gross structure and not to the function of the glands.

Laignel-Lavastine (122) describes tetany as "beginning with a tingling and stiffness of the fingers, soon followed by intermittent spasms of the flexors of the extremities, flushing of the face and a temporary edema of the joints. The tendinous reflexes can be educed and are even markedly increased. Dyspnea, tachycardia, fever, increased salivation, vomiting and diarrhea appear and cause great discomfort because of their severity. Diarrhea is caused by the action of calcium in the intestines during its excretion and is also seen when calcium in large doses is given by mouth. There is bladder irritation and lachrimation, abdominal pain and spasm of the gut and stomach. The clinical picture may simulate cholecystitis."

Trousseau's sign ("main d'accoucheur") is seen on

compression of the arm early in the attack. Chvostek's sign is also very prominent. This consists of a fleeting or prolonged contraction of the facial nerve when tapped just in front of the ear over the auriculo-labial course. Chvostek described three degrees of reaction and designated them Chvostek I, II, and III. Chvostek I is that where the entire facial musculature is involved. Chvostek II is that where only the alae nasi are involved and Chvostek III where the angle of the mouth alone reacts. The sign is not pathognomonic of tetany alone but is seen in tuberculosis, epilepsy and neurasthenia. It is always seen in latent or manifest tetany.

Weiss' sign is also seen. It is a brisk contraction of the muscles of the forehead, eyebrows and eyelids on light percussion of the temporal branch of the facial nerve at the level of the external angle of the eye. The hyperexcitability of the motor nerves when stimulated by galvanic current constitutes Erb's sign. The reaction is most marked during cathode closure when the threshold is greatly lowered and during anode opening when it is correspondingly raised.

There are vasomotor changes during tetany and a dermagraphia and circumoral pallor not uncommon. Paraesthesia and numbness are frequent complaints of an affected person. Both together constitute Hoffmann's phenomenon. The causative factors are the involvements of the motor, sensory and sympathetic nerves as well as the higher brain centres. In fact every nerve cell is affected when it is robbed of calcium. The ciliary muscles of the eye are often seen in spasm during tetany. The effect of therapeutic calcium is

registered directly on the nerve trunks, rendering them incapable of transmitting the impulses which cause convulsions. Magnesium and strontium likewise reduce the hyperexcitability.

In animals the symptoms are analagous to those seen in man. Dogs become anxious, restless, show fibrillary twitchings and a stiff ~~pr~~ staggering gait. Convulsions and hyperpnea up to 250 respirations per minute are seen. The rectal temperature rises. If no treatment is given, the animal dies of exhaustion and emaciation. If the phrenic nerve of an animal is stimulated by the action currents of the heart "cardiac respiration" is present in which the diaphragm contracts with each heart beat. Tetany in dogs is not due to hyperpnea alone or to anoxemia or the blood changes resulting therefrom.

Bryan and Garrey (34) describe an insidious cycle of contributing factors in the post-parathyroidectomy tetany of dogs. There is the usual low blood calcium, hyperexcitability and fibrillary twitching. These lead to a rise in temperature and panting which in turn causes overventilation, alkalosis and eventual tetany. Bryan and Garrey found little change in the pH of blood or tissues until just prior to the onset of tetany. The temperature rises slowly before the development of the fibrillary twitchings but rapidly after onset and reaches a maximum of 44°C . The shift to alkalinity causes a rise of pH and a decreased ^bcaron dioxide tension of the blood due to overventilation.

In these dogs, the existing irritability was due to diminished calcium and was augmented by the alkalosis due to panting. The summation of the two either precipitated an attack or intensified one already in progress. Equal or greater changes in the acid-base balance or an equivalent rise of temperature in normal dogs failed to produce an attack.

Tetany in dogs occurs when the ratio of calcium to phosphorus in the blood is equal to 1.0. This is the only constant chemical factor. Dogs whose parathyroids have been removed are more susceptible to infection than normally. MacCallum (134) saw no tetany in dogs nor any symptoms until twelve hours after operation. Then the twitching of the muscles began. A continuous quivering and vibration of the tense muscles ensued and was interrupted by violent convulsive jerks. The body became rigid, the jaws snapped and violent clonic convulsions enveloped the animal. The temperature rose because the heat of the muscles could not be dissipated fast enough. (The panting was an ineffective effort to dissipate heat.) Lactic acid appeared in the urine in large amounts due to the increased muscular effort. Death occurred during a seizure or was delayed and resulted eventually from emaciation and exhaustion when the twitchings were milder. Dogs in tetany when perfused through the leg with blood from a normal animal became normal in that extremity. If the femoral vessels were anastomosed with their own stumps, tetany recurred as soon as the leg was flooded with the animal's own blood.

When calcium was removed from the perfusing blood by dialysis, there was no change in the tetanic animal.

In cats, during tetany there is a shaking of the paws and rhythmic swimming movements. At first there is a loss of appetite and an alteration of disposition. The animal becomes depressed and sluggish. The limbs and tail become progressively stiff and begin to quiver. Eventually clonic contractions of the extremities are seen. The serum of parathyroidectomized cats used in perfusing frog hearts acted as did the blood of similarly treated dogs when perfused through normal animals. Like results are obtained when calcium-free Ringer's solution is the perfusing fluid. There is no demonstrable effect in normal animals but partially parathyroidectomized animals show tetanic symptoms.

Following parathyroidectomy in man, the blood calcium drops below 7 mg. per 100 cc. When the level of blood calcium drops to 5 mg. per 100 cc. convulsions appear. There is no absolute change in the sodium or potassium content but there is a decrease in the ratio of calcium to potassium. Gross and Underhill (93) believe that the ratio of calcium to potassium is more important than the actual concentration in maintaining normal neuro-muscular conditions. A change in one ion causes a compensatory shift in the other. The urine volume falls off about thirty per cent and the phosphorus excretion is decreased as much as sixty two per cent.

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PHILIP H. KATZ, M.D., F.R.C.P.

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Latent tetany or spasmophilia is due to the hypofunction of the parathyroids. The blood calcium is somewhat lowered, the electrical thresholds of muscular reaction drop and the patient is at the border which separates the normal condition from tetany. Any strain on the calcium metabolism acts as a fuse to set off active tetany. Oestrus, menstruation, pregnancy, lactation and acute febrile disease create a need for added calcium during these states and the calcium intake should be increased in the diet.

Apparently the foetal parathyroid does not function before birth for if it did the mother should be under no strain to maintain calcium levels and should be able to draw on the secretion of the embryonic glands. The permeability of the placental villi to the hormone has never been proven, however. Ewes do not usually become pregnant after the removal of the parathyroids. When, as rarely happens, they do become pregnant the foetus dies long before term. Oestrus in the parathyroidectomized rat is increased twelve per cent in length of the cycles. Such rats seldom give birth to viable young.

Young animals are more susceptible to tetany than mature animals. The additional need for calcium during growth probably explains the finding.

Tetany may occur spontaneously after thyroidectomy but the view is held almost universally that all forms are associated with the removal of the parathyroids. Some parathyroid tissue may remain after parathyroidectomy and tide the animal until the growth of hyperplasia has taken place.

Pyloric stenosis interfering with the absorption of calcium from the intestine may bring on the syndrome. The differential diagnosis of epilepsy and tetany is sometimes difficult. Voegtlin (203) declared in 1917 that the offspring of partially parathyroidectomized animals have hyperexcitable offspring.

Idiopathic tetany in children is probably due to atrophy or pathologic degeneration of the glands, either congenital or occurring soon after birth. The condition was first described by Erb in 1874. The contractions are tonic rather than clonic but the carpopedal spasms are identical with those seen in other forms of the disease.

The relation of the blood and cerebrospinal fluid calcium was constant and led them to conclude that tetany is due to a change of the non-ionized calcium of the body. Their normal values are slightly higher than usually found but they were made over a twenty day period and with a large series of patients. (Average values of Salvesen and Linder - 11.1 mg. per 100 cc. in blood serum. 5.8 mg. per 100 cc. in spinal fluid.) The diminution of circulating calcium caused a relative increase in the sodium of the blood and a disturbance of the calcium/sodium ratio and also of the potassium; calcium ratio except in cases of gastric tetany where the ionic change is due to an increase of the acid carbonate ions.

Cameron and Moorhouse (37) felt that the organic calcium of the blood dissociated only very slowly when the inorganic calcium ion was removed. They stated that parathyroidectomy leads to a drop in the proportion of plasma which is in a diffusible form.

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The Incidence and Severity of Tetany

In view of the large number of operations performed on the thyroid gland of man, the incidence of tetany following removal of goiters is very low. Crile (57) reports 1.3 per cent cases of tetany in 11,508 thyroidec-tomies done at the Cleveland Clinic. It occurred four times as commonly in females as in male patients. Bill-roth, Riverdin and Mikulicz in the early eighties reported a higher incidence but refinement of technique in surgery has lowered the figure in the intervening years.

The severity of the symptoms varies in different mammals and may be a function of the degree of biological difference. In man the symptoms vary with the age and sex and with the degree of calcium deficit at the time of onset. The prognosis is good in latent tetany. In tetany occurring after two years of age, it is likewise favorable unless the condition is complicated by rickets or acute gastrointestinal disease.

The more excitable the animal, the higher is the muscular and nervous tension, and the more severe is tetany. This is illustrated by Vincent (201) in studies of the mor-tality ^{after} parathyroidectomy in Norway rats. The total mortality following operation was 90 per cent. In "gentled" or tamed animals, it was 13 per cent but in wild albinos it was 79 per cent. These figures in themselves prove nothing but suggest a low blood calcium before operation and a consequently diminished reserve.

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Tetany occurs endemically in the large cities of India and Europe (143). A seasonal occurrence in the spring months in India is reported which can be related to the decreased calcium assimilation during the winter months when the character of the sun's rays is changed. In Heidelberg and Vienna, ^{also} tetany seems to occur more frequently in the spring and is probably related to the same cause. There may ^{be} all degrees of severity in the endemic form but it is commonly mild. McCarrison (143) explains the occurrence of parathyroid tetany in goitrous districts of India by the pressure of the thyroid tumors on the parathyroids and consequent atrophy.

There is a very small amount of water in the

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Table FourThe Incidence of Parathyroid Tetany Following Thyroidectomy

Koch (Berlin)	5 times in 1000 operations
Mayo Clinic (Rochester, Minnesota)	1 time in 1200 operations
Frazier (Edinburgh)	8 times in 2000 operations
Crile (Cleveland Clinic)	150 times in 11,508 operations

1871

THE HISTORY OF THE CITY OF BOSTON

FROM THE FOUNDATION OF THE CITY

TO THE PRESENT TIME

BY JOHN B. HENNING, ESQ., ATTORNEY AT LAW

AND EDITOR OF THE BOSTON GAZETTE

AND THE BOSTON ADVERTISER

AND PUBLISHED BY J. B. HENNING

AT THE BOSTON BOOK CONCERN

The Therapeusis of Tetany Other than with Parathormone

Before the isolation of the active principle of the parathyroid secretion, calcium salts were commonly used to prevent, arrest and control tetany. Various impure glandular products were tried with indifferent results. At present it is felt that a combination of calcium and the parathormone is the most effective treatment of tetany. It follows Crile's reasoning (57) that parathormone promotes the absorption of calcium but if calcium is deficient, parathormone will be ineffective. Crile also advises Vitamin D as a stimulant of calcium absorption but he questions the functional permanence of transplants.

In 1925 before Collip's announcement of the discovery of the parathyroid hormone, Cameron and Moorhouse (37) used calcium salts in the treatment of tetany together with milk. They gave small doses five or six times a day by mouth. Calcium and ammonium chloride gave good results by producing an acidosis. Mineral acids were efficacious but not practical for obvious reasons. The relief of the alkaline tendency by ammonium phosphate leads to a retention of phosphorus which inhibits the ionization of calcium when acid salts are given.

Thyroid by mouth was used by Cobb (45) in treating parathyroidectomized dogs. The presence of accessory tissue was not ruled out and may explain the improvement which followed.

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OF THE UNITED STATES OF AMERICA

FROM THE FIRST SETTLEMENTS TO THE PRESENT TIME
BY JAMES M. SMITH
VOLUME I
THE EARLY PERIOD
FROM 1607 TO 1789
NEW YORK: PUBLISHED BY J. B. LIPPINCOTT & CO., 15 N. 2ND ST. 1889

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Greenwald (86) in 1926 gave calcium salts orally to thyroparathyroidectomized dogs. Later he observed that additional calcium phosphate had been laid down in their bones. Still later calcium equilibrium was reached. Luckhardt and Goldberg (129) in 1923 kept a parathyroidectomized dog alive for a long time on a meat diet with the addition of 1.5 gram of calcium lactate per kilogram of body weight per day. Luckhardt and Rosenbloom (130) claimed to have cured tetany and prevented recurrences by means of intravenous Ringer's solution. Calcium chloride in massive doses of ten to fifteen grams every four hours was needed to maintain a child of four months free from symptoms of tetany.

Biedly(21) felt that life could not be prolonged indefinitely with calcium alone. He managed to control active tetany in dogs with 1.5 grams of calcium chloride per kilogram of body weight per day. Boyd, Austin and Dacey (29) found it necessary to give one gram of ammonium chloride a day to parathyroidectomized dogs to reduce the frequency and severity of their symptoms. The means by which acid forming salts work is by rendering deposit and circulating calcium more diffusible. Survival is prolonged but there is never complete recovery with ammonium chloride medication alone.

Wenner and Swingle (186) reported the effective use of oral strontium lactate in 1926. They felt that it had the dual effect of decreasing the permeability of the intestine to calcium and of a sedative acting on the nervous system.

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In 1927 Wenner (211) reported the use of oral ammonium chloride to prevent tetany in parathyroidectomized dogs. They recovered from active tetany in one and a half hours after the ingestion of one to two hundred cubic centimeters of five per cent ammonium chloride. After thirty to forty days of such treatment, they could safely be given a meat diet. Wenner ascribed the effect to the acidifying action of the medication on the blood and a consequent rise in calcium.

Greenwald (87) in 1929 used the same salt to prevent tetany in human subjects. He believed there was a diminution of reflex excitability by acidosis and an increased excretion of phosphorus, sodium and potassium. Luckhardt, Brannon and Waud (131) used magnesium chloride likewise and claimed increased mobilization of calcium resulted. Hjort (102) of the Parke, Davis laboratories used calcium lactate, calcium chloride and calcium glycerophosphate in equivalents of 0.2727 gm. calcium oxide per kilogram of body weight per day with good effect. Roe and Kahn (172) maintain that calcium lactate is as effective as when given orally as intravenously. Bauer and Ropes (14) failed to get rises of blood calcium comparable with the 108 per cent rise of Roe and Kahn after 5 grams of calcium lactate but agree that massive doses are effective.

Kunde, Oslund and Kern (119) controlled tetany in fifty five per cent of 31 dogs by experimental hyperthyroidism. The symptoms were aggravated and the serum calcium

dropped when thyroid was given. As long as the medication was given the dogs could be fed two to four hundred grams of meat daily without the appearance of spasms.

It may be that the spontaneous recovery from tetany is due to an acidosis resulting from the hyperactivity of the muscles during an attack. The deposit calcium is then made diffusible and is converted to the circulating type. The animal is maintained by this additional calcium until hypertrophy of gland makes the cycle unnecessary.

It seems natural to expect that implantation of functioning parathyroid tissue would annul the effects of extirpation of the gland. Studies to determine the minimum amount of tissue needed to protect an animal have led to varying conclusions. Eiselsberg in 1892 advanced the theory that extirpation was not an entirely valid means of proving the endocrine nature of the gland. He felt that only when glandular tissue functioned after ^{being} grafted was such a conclusion warranted. Transplantation of the parathyroids was first done successfully by Biedl (21). He transplanted parathyroid tissue to the spleen, removed the parathyroids left in situ and did not observe any symptoms of tetany. On extirpation of the transplant, the animal died in tetany within twenty four hours. When tetany occurred before splenectomy, the graft appeared to have degenerated when it was sectioned. In tetany-free animals, it had "taken" and the grafted tissue alone was ample to maintain life and protect against spasm. Halsted and Evans (94) confirmed Biedl's finding that only the necessary amount of grafted tissue lived. The remainder necrosed. The average size

of the surviving grafts was 0.5 x .25 mm.

Jung (116) in 1927 implanted the glands of dogs into rabbits and found that they functioned. Collip (50) speaking before the Harvey Society of New York in the same year announced that a single glandule was sufficient to protect a human. Marine (138) recommends the thymus as the optimum site for implantation. Lahey (121) advises immediate reimplantation following inadvertent removal during thyroidectomy and cites many successful cases where that procedure was followed. At operation, if the parathyroids are removed he carefully locates them and places them in the sternomastoid muscles.

Bandler (7) believed that two glandules must be left at operation. If only one remains the patient is dangerously near the threshold of tetany especially in times of increased calcium need. The efficiency of the components of the parathyroid system has been studied and it is thought that one gland may be more effective than another in regulating blood calcium. It is possible that one glandule may be slower than another in activity but is probably not less potent than others in the same animal. Homotransplants (from other members of the same species) are less liable to "take" than are autotransplants.

Grafted human tissue is effective in rats. It liberates a non-specific material mitigating the effects of parathyroidectomy and the substance may be identical with parathormone.

Grafts to the medullary cavities of the bones have been successful. The first filial generation of rats in whom grafts have been implanted after the loss of the parathyroids show some predisposition to tetany.

In thyroidectomies, stripping the posterior capsule does not guarantess^e safety for the parathyroids. Crile (57) routinely leaves the parathyroid in the stump of the thyroid where a rich blood supply aids in the establishment of permanent function. Some of Crile's transplants are active five years after operation.

When heterotransplants are made, the donor should be near the age and sex of the recipient. The graft must be active before implantation else it will not spring into activity in the new host. Female donors are undesirable since pregnancy and associated conditions place excessive strain on the remaining tissue. Eclampsia may be associated with parathyroid deficiency. In the Union of Socialist Soviet Republics, glands for grafting have been taken from bodies soon after death. They function for a time but no data are available as to the permanence of their activity.

The abdominal wall between the muscles and the peritoneum is a good site but the tibia, thyroid stump and spleen are not less desirable. Brown⁽³³⁾ reported a case in 1911 in which implantation was made in order to treat tetany, Ox glands were macerated and mixed with normal saline. The preparation was injected subcutaneously into the abdomen but proved ineffective. Tissue from a monkey and from an ox functioned for a short time but the effect was not permanent. The woman was maintained free from tetany with calcium until her death.

The Secretion of the Parathyroid Glands

The proof of a secretion elaborated by the parathyroid glands is of recent date. The active principle was long suspected to exist but it was of more academic than clinical importance. When its significance was learned and its influence on calcium metabolism established, it was widely used in treating parathyroid disease. The administration of the extract alone or to supplement calcium compounds placed parathyroid tetany among the diseases whose terrors have been dissipated by the biochemist.

Extracts had been made and used in substitution therapy for years but consistent results were not obtained until the work of Hanson, Berman and Collip was known. Moussu in 1898 claimed to have arrested postoperative tetany in dogs by subcutaneous and intravenous injections of a preparation of equine parathyroid tissue. Vassale in 1905 introduced "parathyroidin" to the scientific world. It was thought to have a favorable effect when used in human tetany. In 1909 Berkeley and Beebe made and used an acetic acid extract with curative properties. The effect of this preparation varied beyond the limits of clinical application. The makers claimed that the principle fraction was a nucleoprotein and could be extracted with physiological saline.

Hanson (98,99,100) in 1923-24 published a series of papers describing the preparation and use of a weak hydrochloric acid extract in the tetany of experimental animals and man.

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Berman (18) in 1924 obtained a crystalline substance from beef parathyroids after acid-alcohol extraction and the removal of lipoids and proteins. The substance obtained was soluble in Ringer's solution and when used intravenously raised the blood calcium, decreased the intensity of Erb's sign and seemed almost specific in the treatment of parathyroid tetany. In the same year, 1924, Scharpey-Schafer (175) failed to find the hormone according to his own statements.

Collip (47) in 1924 prepared an extract by treating fresh or acetone preserved glands with five per cent hydrochloric acid. Later (52,53) it was purified and standardized. The proof of its activity was demonstrated by the consistent prevention or relief of tetany in parathyroidectomized animals under the most rigid conditions. The blood calcium was always raised in the test animal. The therapeutic effect of the preparation could be predetermined by its calcium raising or mobilizing effect in normal dogs.

A long purification is necessary in the preparation of the extract for clinical use. Repeated solution and precipitation at an isoelectric point contributes materially. Little is known about the chemistry of the Collip preparation. The purest lots contain some inert material. It can be inactivated by proteolytic enzymes such as pepsin or trypsin and is evidently a protein derivative, possibly a polypeptide.

It has been shown that it is not species specific, that it is not in the control tissues nor is it a chemical artefact. Collip (50) speaking before the Harvey Society in 1927 asserted it to be a protein substance. The common protein reactions, the xanthoproteic, Millon's, the biuret, the ninhydrin and Hopkin-Cole's are positive. The Molisch carbohydrate and the orcinol-hydrochloric tests for pentoses are negative. Sulfur and iron are present. The air dried powder contains 14.5 per cent nitrogen. It is stable and the purified solid is soluble in absolute alcohol only to one-tenth per cent. The extract can be destroyed by boiling with 10 per cent hydrochloric acid or with 5 per cent sodium hydroxide. It can not be dialyzed through semi-permeable membranes. It can be removed from solution by Norit and the Folin-Wu tungstic acid reagents used in precipitating proteins from blood. In many respects it resembles insulin. From the above description, it may be concluded that it is a protein complex with little or no associated carbohydrate or lipoid material.

Collip (47) described his original material and its preparation thus: Fresh ox glands when slaughtered are separated from fat and connective tissue, chilled and frozen. When used they are placed in large Pyrex test tubes with equal volumes of five per cent hydrochloric acid. If acetone preserved glands are used, three per cent hydrochloric acid will suffice. The tubes are placed in a boiling water bath for thirty minutes to an hour. The mass is broken up with a fine stirring rod until all the material is finely

divided or in solution. The extract is then diluted with four parts of water and cooled. The fat is removed mechanically. The solution is made alkaline to a pH of 8.0-9.0 with sodium^{hydroxide} which dissolves the suspended material. Hydrochloric acid is added with constant stirring until precipitation is considerable. A rapid filtration is then possible and the pH is adjusted to 5.5-5.6. The precipitate is dissolved in weak alkali and hydrolyzed as before. The procedure is repeated as long as any active material can be obtained from the filtrate. The removal of active material is tested by making the solution acid to Congo red and saturating with sodium chloride until appreciable precipitate is formed ("salting out"). The active substance flocks to the top of the liquid, whence it is transferred to a filter and separated from the mother liquor. Again it is dissolved, (this time in weak sodium hydroxide) centrifuged and adjusted to a pH of 4.8, At this isoelectric point, it is filtered or centrifuged and dissolved in hydrochloric acid. The series of procedures is repeated until the filtrate is devoid of color. The residue is dissolved in hydrochloric acid at a pH of 3.0 and filtered through a Berkefeld candle to remove suspended bacteria.

Hanson (98) in 1923 described his original extract as aqueous, faintly acid and containing protein. Its ash was rich in phosphorus and contained sulfur. The proteins were soluble in dilute sodium hydroxide. The preparation was soluble in distilled water at 40° C. There was a marked Millon's reaction which indicated the presence of a phenol group. Xanthine, by actual analysis, was found to be the

predominant purine. Precipitates isolated from boiled hydrochloric and sulfuric acid solutions yielded crystals with a tendency to form double horns. Their melting point was 120° C. Others were large, ~~the~~ monochromatic three sided bars which lost their crystalline sheen at 148° C. They charred at 270° C. Hanson did not claim to have a better preparation than Collip's but believed it was more concentrated. It was active after fifteen months on ice.

Tweedy (198) in 1930 made an extensive study of what he called the "plasma-raising calcium principle of the bovine parathyroid glands". He prepared various extracts which had previously been described. Collip's extract he found to be a light grey, amorphous powder of complex protein nature. It could be removed from acid solution by half saturating with ammonium sulfate ~~or~~ by saturating it with ammonium chloride. The preparation of Fisher and Larson (78) was found to be very stable as indicated by indefinite preservation by tricresol in an ice box when ~~in~~ neutral solution.

The acetone-picric acid extract of Davies, Dickens and Dodd (60) made without preliminary hydrochloric acid extraction was insoluble in water but could be easily converted to the hydrochloride and in that form it was soluble in water. Tweedy proceeded to make an extract by hydrochloric acid extraction of acetone desiccated and defatted glands. The active principle was partly soluble and stable in liquid ammonia and in ethyl lactate. Irradiation for two or three hours did not alter its effect.

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It was very resistant to heat in phenolic solution but was inactivated by hydrogen chloride gas in absolute alcohol. In 1931, Tweedy (199) obtained a potent fraction by extraction of fresh bovine glands with aqueous 90 per cent phenol.

The immediate effect of the intravenous parathormone is a rise of the blood pressure. It soon sinks back to the normal level. The rate of respiration is increased and there is a transitory diuresis due to the effect of the extract on the renal epithelium. Massive doses cause a rise in body temperature. It has been suggested that local application increases the contraction of the intestine and uterus and stimulates the dilatation of the pupil. The serum calcium rises gradually for a number of hours following injection, then plateaus for a short period and falls to the initial level. The height and duration of the curve varies directly with the size of the dose. Single doses, unless they be massive, have little effect. When repeated in small doses, there is a pyramiding effect ^{whose} ~~which is~~ sum is greater than a single large one. If the rise in blood calcium is greater than fifty per cent of the initial figure, there is vomiting. This alone ^{the dosage is} ~~is~~ not serious but if continued, the calcium may rise to 20 milligrams per 100 cc. of blood. Death from hypercalcemia occurs in two or three days. If the hypercalcemia is not maintained recovery is uneventful. Brown-Sequard suggests that the toxic effects of glandular extracts in large doses may be due to thrombo-kinesic substances. Sodium bicarbonate is the best known treatment for hypercalcemia produced in this manner.

The effect of parathormone on children is variable (106). There is a diminution of calcium retention in normal and rachitic children. After continued dosage, it is necessary to raise the amount given because of an acquired tolerance due to the increase of serum protein. Intercurrent infections during tetany in children also make larger doses necessary.

Allardyce's studies (3) give the best available information of the results to be expected in laboratory animals. Cats, he found, show little or no rise in serum calcium after massive intravenous doses and were concluded to be unfit for assay purposes. An acid medium in vivo is not necessary since the potency of the active principle was not altered by making alkaline to phenolphthalein. Acid hydrolysis freed the active principle but if carried too far, caused inactivation. The rate of destruction increased with the strength of the acid used. The most potent extract was made by hydrolyzing the glands for forty five minutes with 1.5 per cent acid.

Allardyce also found that the glands exhibited a marked buffering action. Temperatures of 80-100° C. were needed to free the active principle and to destroy enzymes which if allowed to remain would in time inactivate the preparation. Saponin, as used in Harington's method for purifying insulin, was valueless in separating the active and inactive fractions. It completely destroyed the hormone. Gradual approach from the acid side to the isoelectric point

yielded an amorphous precipitate of both fractions.

Dogs responded better and more uniformly to parathormone on a meat diet than ^{on} ~~to~~ an oatmeal diet but either diet was improved by the addition of cod liver oil to aid the absorption of calcium. Extracts of oatmeal did not give evidence of an interfering or antagonistic factor. The delay in response was due to an increased tolerance rather than to the depletion of available calcium. Intravenous administration of parathormone gave a greater and more rapid response in four to eight hours than when given intramuscularly or subcutaneously.

The means by which parathormone effects a rise in calcium is still questioned. It is most probable that it causes a mobilization of deposit calcium rather than an inhibition of the excretion of that substance. Absorption of intake calcium from the gastrointestinal tract is hastened by the extract. That there is little direct effect in the stomach is evidenced by the lack of increase in gastric juice calcium when enough parathormone was given to raise the blood calcium to 19 milligrams per 100 cc. In dogs with a Pavlov pouch, there is no change in the rate of gastric secretion after parathormone administration.

Peters and Van Slyke (161) believe parathormone gains its effect by increasing the solubility of calcium and phosphorus in the serum. Cantarow (42,43) says that the best index of parathormone activity is a simultaneous determination of blood and spinal fluid calcium. Both fractions of blood calcium are affected but the greatest rise is in the diffusible portion. In some cases where the calcium level of blood is

normal, there is a preliminary rise in the diffusible-non-diffusible ratio. This is followed by a more marked and prolonged drop below the normal level. The variations, Cantarow shows, bears no relation to the total serum calcium. Morgulis and Perley (148) aver that there is no demonstrable effect on the spinal fluid calcium. Personal findings agree with those of Cantarow.

The first case in which Collip's extract was used clinically was that reported by Lissner and Shepardson (127) in 1925. The patient was a woman of thirty with an adenomatous substernal goiter. In the course of its removal, three parathyroids and possibly a fourth were removed. Tetany appeared in a few days. No calcium was given by mouth for three weeks after operation except one gram of calcium lactate before the first injection of parathormone. The patient was fed the usual ward diet. Excellent results in the control of tetany were observed and it was concluded by Lissner and Shepardson that parathormone was a specific treatment of parathyroid tetany. The preparation of Eli Lilly and Company was used (See Appendix B).

Hoag and Rivkin (105) treated four cases of infantile tetany in 1926 with Collip's extract. The improvement was rapid and normal calcium figures were obtained in twenty four to forty eight hours. Continued daily subcutaneous injections maintained the blood calcium level. The dosage was 5 units per kilogram of body weight for each milligram rise of calcium desired.

There is a small pond in the middle of the field.

The pond is very small and is only a few feet deep.

It is surrounded by a low wall of stones and is very old.

The water in the pond is very clear and is very pure.

It is very good for drinking and is very healthy.

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Nitzescu (151) in 1929 injected parathormone into the subarachnoid space after withdrawing an equivalent amount of spinal fluid. There was a rise in serum calcium but it amounted to only 1.8 - 3.0 milligrams. He concluded that the molecule of parathormone was smaller than that of insulin and more diffusible since insulin when injected into the spinal fluid does not produce hypoglycemia. Swale Vincent (201) declared that parathormone injected into the maternal circulation produced a rise of foetal blood calcium. Whether the rise in foetal calcium is a primary or secondary result of the parathormone is uncertain since there is no evidence for the permeability of the placental boundary to that substance.

Snell (179) in 1925 claimed that the hormone was not effective in chronic tetany. The lack of response in refractory cases we would now ascribe to an increased tolerance of the subject rather than to a low potency of the extract. Calcium lactate or related compounds will not alone raise the blood calcium and with parathormone may be ineffective if absorption is faulty.

That parathormone may be harmful in conditions requiring bone regeneration is suggested by an increase of urinary calcium output following its use. (Fine and Brown, 77) However, the effect of parathormone and ammonium chloride on calcium excretion is more than can be explained as the sum of their activity. Albright, Bauer and Ropes (2) confounded the statements of Fine and Brown by showing in 1929 that parathormone had no effect in decalcifying ossifying hematoma.

The idea of Greenwald and Gross (88,90) that the parathyroid hormone draws calcium from non-osseous tissues and then from the bone to replace it is interesting but unconfirmed. Bacq and Dworkin (5) showed that the absence of central nervous system impulses does not influence the response to parathormone. They observed typical responses in sympathectomized dogs and cats. Hfort and Eder (103) claimed to have seen good results from the combined use of parathormone and thyroid preparations after parathyroidectomy but recommend transplants if extensive resection is necessary.

Parathormone in ordinary doses does not affect the heart. When given to the extent that it increases blood viscosity, it causes a fine tremor, atonia and increased salivation. The heart beat rises in frequency, there is arrhythmia and premature beats can be heard. Changes in blood pressure may result. Because of the symptoms, it is inadvisable to give parathormone to cardiac patients (Edwards and Page, 70).

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The Standardization of the Parathyroid Hormone

The method of standardizing the parathyroid hormone by the production of ~~a~~known and measured hypercalcemia is the best available but it leaves much to be desired in accuracy. Allardyce (3) objects to the use of cats in parathyroid assay since their response is so slow. He, as does Collip, prefers dogs and believes that the hormone acts best when the animals are fed on a meat diet. The diet is improved as a supportive to the parathormone when cod liver oil is also given. For clinical use, Berkefeld sterilization was done after the preparation had been standardized by Allardyce.

The unit of parathormone is expressed as the amount which will elevate the serum calcium of a normal ^ttwenty kilogram dog 5 mg. per 100 cc. in fifteen or sixteen hours. The amount is conveniently contained in one-twentieth of a cubic centimeter. (1 cc. = 20 units) The material to be tested is dissolved in normal saline, injected subcutaneously into the dog and the blood withdrawn fifteen hours later. Coagulation is prevented by heparin. Potency tests are made with at least ten dogs and the results averaged.

Burn (36) feels that no real standardization is possible since there is no standard preparation available for comparative purposes. He recommends the following procedure as the best available method: At six p.m. injection of appropriate doses is made in ten 20 kg. dogs. At 9 a.m., the blood is drawn and analyzed. If the average rise is five milligrams, the dose injected was one hundred units.

THE HISTORY OF THE UNITED STATES

The history of the United States is a story of growth and development. It begins with the first settlers who came to the continent in search of a new home. These settlers were faced with many challenges, including a harsh climate and a lack of resources. Despite these difficulties, they persevered and built a new society. Over time, the United States grew from a small colony into a powerful nation. It has been shaped by the dreams and sacrifices of its people, who have fought for freedom and justice. The history of the United States is a testament to the power of the human spirit and the ability of a nation to overcome adversity.

The early years of the United States were marked by a period of exploration and discovery. Explorers like Christopher Columbus and John Cabot opened up new worlds for the world. They discovered new lands and resources, which led to the establishment of colonies. These colonies were the first steps towards the creation of a new nation. The settlers who came to these colonies were diverse in their backgrounds and beliefs. They brought with them the knowledge and skills of their respective homelands, which helped them to build a new society. The United States was born out of the struggles and sacrifices of these early settlers.

The United States has a rich and diverse history. It is a country that has been shaped by the dreams and aspirations of its people. It is a country that has fought for freedom and justice, and has emerged as a powerful nation. The history of the United States is a story of growth and development, and it is a story that continues to inspire and motivate people around the world. The United States is a country that has the potential to make a positive impact on the world, and it is up to us to realize that potential.

No information is given by Burn as to the interpretation when the rise is less than five milligrams, so the assay has nor more than a rough quantitative significance. Bleeding is from the ear vein from which the hair has been clipped and shaved while it is dry. The ear is rubbed between the fingers to make the vein stand out. A small incision is made with an eye knife and the vein held at the base of the ear. The drops fall freely and no discomfort is experienced by the dog. Ten cubic centimeters are collected in a 15 cc. centrifuge tube which has been cleansed in sulfuric-dichromate cleaning solution and thoroughly rinsed in distilled water. The tube and contents are kept at 37° C. by floating in warm water. The clot is detached with a platinum wire and the tube and contents spun in the centrifuge until four cubic centimeters of serum can be obtained. Analysis is by the Kramer-Tisdall modification of the Collip method. (See Appendix C)

Stewart and Percival (182) recommend the use of cats in parathyroid assay. Their procedure requires the intravenous injection of the preparation in cats anaesthetized with ether and paraldehyde. They claim a rise in blood calcium will be noted in one to two hours. The cat is weighed while under anaesthesia. A trachea tube is inserted and the animal forced to breathe through a Woulff bottle containing ether. Paraldehyde to the amount of one gram per kilogram of body weight is administered by stomach tube. The carotid artery is prepared for taking blood by freeing it from the main nerves of its sheath and clearing it

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from adjacent tissue cephalad to a point where the thyroid branches leave. The branches may be divided between two ligatures close to the origin. The main artery is tied off and after being clamped below ~~is~~ divided between the ligatures and the point of origin of the branches.

Injection is made by a cannula in the femoral vein. A sample of blood is taken from the carotid when all preparations have been made and the parathormone is injected immediately after. Other blood samples are withdrawn one to two hours later. Stewart and Percival observed a rise of two milligrams per hundred cubic centimeters after the injection of ten units of parathormone.

Great variations have been reported in the response of cats and dogs used in assay. In view of the disparity of results, the above methods can not be accepted and used unequivocally.

The use of calves is reported by Robison and his associates (171) in standardization of parathyroid preparations in spite of Taylor's statement (188) that no effect is manifested in the herbivora. Robison admits that the effect in calves is less sensitive though none the less typical of that seen in man or laboratory animals. Thompson (191) in 1930 reported an anti-growth factor in acid-alcohol extracts of the gland and suggests that it may be utilized in standardization procedures. The extract when injected subcutaneously in young rats seemed to retard growth. A similar retardation was noted when injected into Jensen rat sarcomata. The growth of cress was retarded in proportion to the concentration of the extract. Since the results

are identical when an acid-alcohol extract of muscle is used, the anti-growth factor seems less desirable for use in assay than the methods of Allardyce, Burn and Stewart and Percival.

Hanson (100) in 1928 insisted that the parathyroid extract for clinical use should be standardized against known hypocalcemia. He recommended the use of smaller units in order to avoid the dangers of high blood calcium. Hanson used dogs after finding that relatively small doses of his parathyroid preparation would restore parathyreoprivie dogs to their normal condition.

Hyperactive Conditions of the Parathyroid Glands

The conditions resulting from hyperfunction of the parathyroid glands are quite as refractory in their response to therapy as is tetany. In 1891, von Recklinghausen, a pupil of von Virchow described the condition now known as osteitis fibrosa cystica. His description was adequate but no etiology was suggested by him at the time. Since that time, this and other bone diseases have been shown to be caused by increased parathyroid activity. Much of the present day research centering about the parathyroids is concerned with bone dystrophies.

In 1903 the enlargement of the parathyroids seen in osteomalacia (adult rickets) was noted. In 1906 the first true parathyroid tumor was found. Observers then began to look for neoplasms of the gland and in 1919, there were thirty authenticated cases in the literature. Most parathyroid tumors are benign and recognized only at autopsy. In the early days, no differentiation was made between adenomata and hyperplasia.

Erdheim in Vienna noted that following extirpation of the parathyroids of immature rats by cautery, calcification was impeded and in some cases ceased altogether. The teeth of the animals became transparent instead of white and broke easily. Interference with calcification did not end with imperfect dentine but extended to the long bones. Fractures healed very slowly and a soft callus was formed. When Erdheim implanted bits of appropriate glandular tissue, the calcification was resumed but only after necro-

THE HISTORY OF THE UNITED STATES

The history of the United States is a story of growth and change. It begins with the first settlers who came to the shores of North America. These early explorers and settlers faced many hardships, but they persevered and built a new nation. Over the years, the United States has grown from a small colony to a great power. It has fought many wars, both at home and abroad, and it has made many contributions to the world. The story of the United States is a story of hope and achievement. It is a story that inspires us to strive for a better future.

The early years of the United States were marked by struggle and uncertainty. The first settlers, who came from Europe, found a land that was both beautiful and hostile. They had to learn to live with the native Americans, who were often at odds with them. The settlers also had to learn to live with the harsh weather and the lack of resources. Despite these challenges, they managed to establish a new society. They built farms, towns, and a government. They fought for their rights and for the rights of others. They created a nation that was based on the principles of liberty and justice for all.

As the United States grew, it became more and more diverse. People from all over the world came to live in the United States. They brought with them their own cultures, languages, and traditions. This diversity made the United States a richer and more interesting place. It also made it more difficult to govern. There were many different interests and opinions, and it was often hard to reach a consensus. But the United States managed to overcome these challenges and to create a government that worked for everyone.

The United States has come a long way since its first settlers. It has become a world leader in many fields, including science, technology, and the arts. It has made many contributions to the world and has helped to improve the lives of many people. The story of the United States is a story of progress and achievement. It is a story that shows us what is possible when we work together and when we strive for a better future.

sis of the central part of the graft. The^{re} was a survival of the marginal layers and in some cases an increase in their width. In the teeth dentine replaced the uncalcified matrix. Ossification was reestablished when the graft lived. Until the findings of Erdheim were known no connection between bone growth and parathyroid activity had been recognized. Even in 1917 the relation was not well understood for in that year, Voegtlin (203) stated that hyperparathyroidism was unknown.

Woelfler distinguished parathyroid neoplasms either as foetal adenomata (intrathyroid tumors) or as juxta-thyroid (glycogenous) goiters. The difference between thyroid and parathyroid tumors is easily seen on microscopic examination. Grossly the appearance is the same.

Much attention was given to hyperparathyroidism as such after 1926 when Mandl of Vienna (1926) began to study von Recklinghausen's disease. Parathyroid extracts had been administered and transplants of tissue made in this disease before its essential nature was known. Both procedures served only to aggravate the disease. Eventually explorations of the glands were made and often adenomata were removed. Improvement followed and the conclusion was made that either hypertrophy, hyperplasia or adenomata was the chief etiological factor in von Recklinghausen's syndrome.

In this disease, osteoclast formation in the bone is stimulated so that the bone is weakened. (Osteoclasts are polynuclear cells concerned in bone absorption.) There is an increased fibrosis of the cells which form osteocytes. The erythrocytes are unaffected although the bone marrow is unproductive.

is overactive and changes in color from red to yellow, The patient shows progressive weakness, loss of muscle tone, anemia, pain in the bones, decrease of deposit calcium and a relative increase of organic matter in the bony structures of the body. There is ^{generalized} hypotonia, diminished sensitivity ^{of the nerves} and hypotonicity of the muscles. Multiple giant cell tumors are not uncommon. There is a rise in the concentration of circulating calcium and a corresponding drop in phosphorus due to mobilization of bone salts by increased parathormone secretion.

Plasma phosphatase is affected indirectly by the increased secretion of the glands. The treatment is directed toward inhibiting parathyroid activity and is sometimes accomplished by ultraviolet light plus a Vitamin D rich diet. The removal of the tumor, if present, is indicated. If successfully done, the patient's strength returns and he is no longer asthenic. Muscle tone increases and calcification is resumed. Boyd, Milgram and Stearns (28) speak of renal, osseous and gastrointestinal symptoms occurring concomitantly. Wellbrook (209) cites the relation of parathyroid tumors or hyperplasia to extensive bone destruction. He notes that tumors occur more commonly in the fibrous capsule of the gland than in the central portion.

Cannon (40) speaks of the growth of hyperplasia in the parathyroids following a low calcium diet. It seems logical that overgrowth should occur while the gland is active in maintaining blood calcium levels. In such cases the normal calcium concentration is found but the calcium is replenished from endogenous sources.

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The giant cell tumors of the bone and the adenomata of the parathyroid seen in von Recklinghausen's disease have a general structure like that of the parathyroid itself with the addition of many large, clear cells. Polymorphism is characteristic and the cells have hyperchromatic nuclei. Mitotic figures are common and the neoplastic tissue may invade the capsule. Fat is often seen. The accumulation of nodules of osteoclasts precedes the formation of the tumors. Multiple brown cysts are seen and with blood pigments form osteoplastomas. There is metaplasia and the microscopic bone architecture is changed. The phosphatase index of the blood drops from 4 to 2.9 and the calcium of the blood increases from 10 to 14 milligrams per hundred cubic centimeters. The blood phosphorus is decreased and the body is as saturated with calcium as in osteomalacia but precipitation depends on the function of ion meeting ion. There is really less bone in osteitis fibrosa cystica than normally.

The teeth are little affected. Normal dentition is retarded but there is no decalcification. The teeth which are fully grown are not involved. Occasionally there is calcification of the parathyroid capsule and it then becomes a bony covering. Albright (1) says that if one considers osteomalacia to be hyperparathyroidism, then osteitis fibrosa cystica is hyper-hyperparathyroidism. In both syndromes after the increase of blood calcium and phosphorus there is renal insufficiency, the kidneys shut down, nephrolithiasis is seen, the phosphorus accumulates

in huge amounts and death ensues. Osteomalacia may be a dietary deficiency disease due to the lack of the fat soluble vitamin and calcium. The addition of these substances to the diet has a curative effect. (Miles and Feng, 146) The clinical factors of importance in the diagnosis of osteitis fibrosa cystica are the presence of bone pain and spontaneous fractures through the giant cell tumors. Kidney symptoms such as are seen in diabetes mellitus confuse the diagnostician. Constipation is troublesome and is caused by the constant relaxation of the smooth muscle of the intestine.

In recent years a pathological approach has been made to the study of the disease. Careful metabolic studies show an increased output of calcium and phosphorus extending to imbalance. The actual calcium output was measured by Albright (1) at the Massachusetts General Hospital in Boston. Among his cases was that of a sea captain, Charles Martin. This patient (Albright et al, 2) was a man who found his stature was decreasing and simultaneously experienced other symptoms of hyperparathyroidism. The concentration of calcium in his blood and urine rose and the urine phosphorus decreased. He showed extensive deformities. There were changes in the appearance of the blood clot. Instead of its normal appearance, the clot became dark red, very friable and showed little retraction on standing. The serum showed haemolysis unless centrifuged because the increased calcium content lengthened the clotting time, Parathormone caused the blood calcium to rise even higher and the blood phosphatase likewise increased the blood

calcium at the expense of the bones.

Other studies of the same nature (2,10,11,12) showed that the classification of bone diseases should be revised with reference to the parathyroids. Osteomalacia, rickets, osteoporosis and osteitis fibrosa cystica seemed to be associated with these glands without any question. That the skeleton served not only as support but also as a calcium store which could be called upon in times of body stress was amply corroborated. No change of muscle calcium or phosphorus has been demonstrated in hyperparathyroidism.

The use of phosphatase, a phosphate-splitting enzyme, in diagnosis is rapidly and widely being adopted. It has the quality of being able to convert organic phosphorus compounds into simpler inorganic forms. While it occurs only in the bone in normal conditions, it is seen in the blood, intestine and kidney when decalcification progresses at an abnormal rate. In diagnosis the index of decalcification is the amount of organic phosphorus which can be split by a known amount of blood.

Irradiated Vitamin D in large doses leads to an increase of blood phosphorus and calcium and eventually to osteomalacia. There is such an increase of osteoid tissue that the trabeculae are covered with it, leaving no room for the osteoblasts or germinal bone cells. They are driven out by the osteoclasts which are naturally antagonistic. The bone pathology of rickets is similar but there the skeleton is still growing and there are simultaneous normal and abnormal processes of bone metabolism.

Richardson, Bauer and Aub (167) characterized osteomalacia as a skeletal disease resulting from decalcification. It can be produced experimentally by stimulating parathyroid hyperfunction. To make a diagnosis of osteomalacia, there must be decalcification, muscle hypotonia, increased serum calcium, increased urinary calcium output, a decrease of serum phosphate and an increased phosphorus output. When excess calcium output could be explained in no other way, Richardson, Bauer and Aub looked to the parathyroids as the cause.

Parathyroid changes are secondary to bone changes. The sequence of events are the following: hyperplasia, osteomalacia, multiple myelomas and carcinomatous metastases to the bone. The pathological fractures cited above then follow. The patient complains of difficulty in walking, shows a slight myelocytic anemia of three million red cells and four thousand white cells and a tendency to cataract formation.

Snapper (178) reported a case of mixed type showing extensive decalcification of the bones attended with great pain. It seemed to be osteitis fibrosa cystica generalisata at the onset but was later identified as a "pseudo-osteomalacic end stage of von Recklinghausen's disease". There was a moderate thyroid swelling and on exploration a tumor of the parathyroid was removed followed by improvement. Bauer, Albright and Aub (12) in 1930 reported a similar case where the parathyroids were normal and the metabolism was similar to that of a person getting parathormone.

Bulger, Dixon, Barr and Schregardus (35) gave calcium orthophosphate but recommend parathyroidectomy as the only permanent treatment. Bodansky, Blair and Jaffe (22) aver that parathormone given over a long period causes a negative calcium balance not demonstrable by x-ray and believe age to be a factor in the formation of bone lesions, especially following injury in young animals and in children. Calcium changes and improvement of the bone dystrophies after partial parathyroidectomy are the corner stones of their proof.

Dragstedt (65) admits that fracture repair is delayed in the absence of the glands but shows that the delay is shortened if calcium is given. He alone believes that parathormone is not indispensable since bone will form in transplants in the bladder of parathyroidectomized dogs if they are given sufficient calcium.

THE FIRST PART OF THE HISTORY OF THE

REIGN OF CHARLES THE FIRST

BY JOHN BURNET

IN TWO VOLUMES

LONDON

Printed by J. Sturges, at the Angel in St. Dunstons Church

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The Relation of the Parathyroids to Other Parts of the Body

It seems fairly evident that the relation of the parathyroid glands to other parts of the body is not specific but only as a part of the general endocrine community. There may be a possible effect exerted by the parathyroids on the total metabolism and growth but it is less marked after simple parathyroidectomy than when the neighboring thyroid is removed as well. Growth, after extirpation of the parathyroids, is retarded in immature animals but less so in males than in females. It was thought at the height of the "toxin" theory vogue that retardation of growth was due to the retention of body poisons. The exact factor which causes it is not known.

As will be recalled, the results of extirpation^{of the parathyroids} are diminution of weight and emaciation from loss of appetite and diarrhea. Identical results are seen when the arteries^{of the gland} are ligated without removal of tissue. There are eventually changes in the hair, nails, teeth and bones. Most animals succumb before such changes are seen. The calcification of dentine and enamel is delayed; the teeth are brittle and the healing of fractures is slowed. However, the latter effect is seen also in animals whose vitamin intake is deficient and may in either case be due to an increase in blood phosphatase.

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Parathyroidectomy, after a year of calcium treatment failed to produce clinical or postmortem evidence of secondary disturbances in other glands. In this respect the parathyroids are like the pancreas in diabetes mellitus. There may be a relation between the parathyroids and carbohydrate metabolism but the proof is not entirely satisfactory. The following facts are very suggestive: (Reed, 164,165)

1. Parathyroidectomized dogs in tetany are hypersensitive to insulin while such dogs not in tetany respond in the same manner as normal dogs.

2. Lactose is effective in lowering the hyperphosphatemia of tetany. Body phosphatase is used in transferring glucose from the blood and a temporary glycosuria is seen during tetany.

3. Reed in 1929 found a decreased glucose tolerance in tetanic dogs but an increased tolerance following thyroidectomy. He managed to prolong life by intravenous glucose in parathyroidectomized dogs. The fasting blood sugar level was unaffected.

4. Insulin caused hypercalcemia and decreased blood phosphate in normal and parathyroidectomized dogs.

Salvesen (173) declared there was only an indirect effect on the metabolism of glucose, claiming that the lowered carbohydrate tolerance was due to the influence of the liver in increasing the storage of glycogen.

It has been thought that thyroparathyroidectomy caused an increase in the formation of erythrocytes.

The first thing I noticed when I stepped out of the car was the cold. It was a sharp contrast to the warm blanket I had been sitting under. I looked up at the sky, which was a pale, overcast grey. The air was thick with a damp, wintry mist. I took a deep breath, feeling the cold air fill my lungs. I was alone in the vast, open space, and it felt like the world was watching me. I walked slowly, my boots crunching on the wet pavement. The sound was rhythmic, almost hypnotic. I felt a sense of peace, a momentary escape from the chaos of everyday life. The city was silent, the streets empty. It was as if time had stopped. I continued to walk, feeling the cold air on my face, the wet ground beneath my feet. I was in the heart of the city, yet it felt like I was in a remote, quiet place. The buildings loomed in the background, their windows reflecting the grey light. I stopped for a moment, looking back over my shoulder. The city was a blur of lights and colors, a distant world. I turned back around, continuing my walk. The cold was still there, but it no longer felt like a burden. It was a part of me now, a part of this moment. I walked on, feeling the cold air on my face, the wet ground beneath my feet. I was in the heart of the city, yet it felt like I was in a remote, quiet place. The buildings loomed in the background, their windows reflecting the grey light. I stopped for a moment, looking back over my shoulder. The city was a blur of lights and colors, a distant world. I turned back around, continuing my walk. The cold was still there, but it no longer felt like a burden. It was a part of me now, a part of this moment.

An antagonism has been claimed by Biedl (21) between the thyroid and parathyroid glands. Falta and Meyers (76) also have observed ~~hyp~~hyperthyroidism after tetania parathyreopriva but believe it is due to a compensatory hypertrophy rather than to identity of function of the two glands. Uhlenhuth (200) advances a theory of the antagonism of thymus and parathyroids. He feels that the thymus can produce tetany in children and less easily in adults. The tetany of pregnancy, Uhlenhuth claims, is due to the increased thymus secretion furnished by the foetus to the mother through the communal circulation. Deficiencies of reproduction are claimed by Riddle (168) and he relates them to a deficiency of calcium. When ox thymus is given, the reproductive cycle becomes normal. The fallacious nature of these ideas is apparent. We can continue to feel that the thymus and parathyroids are related only in their embryological source.

A relation of the gonads and the parathyroids has been suggested because of the hypoparathyroidism which occurs during pregnancy and lactation. The increase of calcium needed by the body at these times is a more valid explanation. Pituitary substance may be beneficial in tetany but there is no other evidence for the relation of the two glands. During tetany there is an increase in epinephrine sensitivity.

More recently any disease in which a drop in blood calcium occurs has been thought to be caused by a parathyroid disorder. In myasthenia gravis and pseudo-paralytic conditions such as myotonia periodica, where there is

severe relaxation of musculature, increased parathyroid secretion is considered the cause. In Parkinson's disease (paralysis agitans) insufficient parathyroid secretion is said to cause the tremors which are characteristic. The deficiency has never been substantiated nor has hyperfunction ever been proved (Bainbridge, 6). R.L. Thompson (192) in 1906 stated:

"There is every reason on morphological grounds to oppose the hypothesis that Paralysis Agitans is chronic progressive hypoparathyroidism as has been claimed." His studies are based on the size and structure of the glands in Parkinson's syndrome.

In conditions of nervous irritability such as epilepsy, chorea, and eclampsia, parathyroid treatment is effective but probably because it aids in the diffusion of calcium rather than because of a primary effect.

In the catatonic-schizophrenic psychoses, it was observed that there was a drop in blood calcium. Bowman (27) used parathormone with several patients without beneficial effect and concluded that there is no relation between parathyroid activity and the schizoid states.

The chief effect of the parathyroids is on the metabolism of bone. Hammett (96) found a disturbance in the chemical differentiation of bone postoperatively in parathyroidectomized albino rats. Analysis showed a decrease in calcium and phosphorus and an increase in magnesium in the bone. He attributed the shift to parathyroid deficiency but found no decalcification when the deficit was long standing. Certain of his patients with hyper-

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trophic arthritis and associated rheumatoid conditions improved after parathyroid therapy.

The papers of Tsai and Hsu (195,196) are interesting. They describe the effect of ligation of the bile duct and colectomy in causing a drop in blood calcium. The operations do not interfere with a further drop in calcium or with the production of tetany after subsequent thyro-parathyroidectomy. They conclude that toxins from the intestine are not the cause of tetany. Ligation of the bile duct alone does not affect blood calcium but the severity of tetany is lessened due to the depressant action of absorbed bile.

Conclusion

It will have occurred to the reader long before this point that a wealth of discordant opinions exist relative to the parathyroid glands. To use the phrase of Hoskins (110), we know the "What" but the "Why" is still before us. Certain facts have been established beyond controversy. The anatomy of the glands is clear, due to the pioneer work of Sandstrom and Gley. The gross comparative anatomy of the parathyroids is as well understood as is that of the skin and bloodvessels.

The manner in which an interchange of blood and lymph is brought about is as well understood and is not obscure after a short study. A study of the vascular elements of the gland gives pertinent information as to the manner in which the secretion is made available to the body. The histology of the gland is clear but the purpose and function of the two types of cells need further investigation. The differentiation between the immature and adult parathyroid glands and the reasons therefore should also be studied.

The development of the branchial pouch organs and the rearrangement of the internal and external parathyroids at maturity has been well demonstrated by the embryologist. Little of interest can be furnished by further research in this field toward a better understanding of parathyroid function. Perhaps the most fruitful studies of the next decade will be those related to parathyroid pathology. A study of the glands at autopsy in cases without presenting

parathyroid symptoms or active lesions might be undertaken with good expectation of profitable results.

We have yet much to learn concerning the physiology of the parathyroids. We are convince^d of the relation of the glands to calcium metabolism but the problems of absorption can not be left as they are. The homeostatic activity of the glands is very significant and warrants further investigation. Fortunately most of the workers in the field are interested in those subjects. Although a few investigators cling tenaciously to the theories of toxin destruction by the parathyroids, it seems improbable that either that principle or acid-base equilibrium can adequately explain the function of the glands.

More study can be practicably made of the obscure types of tetany. The prevention of surgical tetany is largely a mechanical matter and depends on the evolution of careful techniques to be used by the operator during thyroidectomy.

The preparation of a hormone which will be tolerated and which will not require increased and massive doses offers work to the physiological chemist. It is probable that the preparation of a pure and active parathyroid substance will eliminate the toxic effects of increased doses or it may be that the need for massive doses will be eliminated because of the potency of a pure substance. Better standardization of parathyroid extracts seems remote until a standard preparation is available for comparative purposes.

Work is proceeding rapidly in Europe and the United States in the study of the hyperactive conditions of the parathyroid gland. Regularly reports appear in the medical literature describing progress toward facilitating the diagnosis and treatment of the bone dystrophies.

It may^{be} that parathyroid phenomena are due to changes in the permeability of the cell membrane to calcium. If this be true, the entire field of neurophysiology may need to be revised because of the changing permeability of the choroid plexus under varying conditions. The permeability of the arachnoid membrane to parathyroid secretion and the methods of determining small amounts of parathyroid hormone in the blood and spinal fluid may well be studied for purposes of diagnosis. Reactions involving calcium are slowed so greatly without the parathyroids that it is evident that the hormone is a valuable catalyst.

The field of comparative physiology of the parathyroids is quite untouched and interesting to speculate about. If the medium in which life is carried on determines the necessity for the parathyroids, an extensive problem presents itself. Experimental pathological studies might be undertaken with reasonable hope of productive results. The question of depressed function and the attendant lethargy during hibernation in certain animals may be correlated with the winter hypertrophy of the parathyroids.

The above problems are cited because they suggest a few of the approaches to research that may be attempted without duplicating work already in progress or now completed.

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Whatever we accept or reject, it is clear that the parathyroids are a potential source of grave or fatal ill health. To the clinician, the chemist and to the surgeon the glands offer a puzzle and a challenge. May time grant the patience and fortitude necessary to a solution.

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Appendix A.

From Classic Descriptions of Disease p. 246
 by Ralph H. Major, M.D.
 Charles C. Thomas, 1937

TetanyJohn Clarke

John Clarke, the son of John Clarke, a well-known obstetrician, was born in 1761. The younger Clarke lectured on midwifery at William Hunter's school and at St. Bartholomew's Hospital. He soon became the leading obstetrician in London but later devoted himself to the study of diseases of children. In 1815 he published his Commentaries of some of the most important diseases of children, which contains what is probably the earliest account of infantile tetany. He died in 1815.

His younger brother, Sir Charles Mansfield Clarke, was a very distinguished obstetrician.

CHAP. IV

ON A PECULIAR SPECIES OF CONVULSIONS IN INFANT CHILDREN*

There is one case of convulsive affection, which is more apt to be overlooked than any other, because the symptoms are not at first very violent, so as to attract the attention of parents or nurses. It is often mistaken and treated as some other disease, even by medical men;

* Clarke, John, Commentaries on Some of the Most Important Diseases of Children (London, 1815), pp. 86-90.

and the true character of it has been little known, even to practitioners generally conversant with infantile disorders: it is therefore less likely to be detected by those who have bestowed little or no attention upon them.

This convulsive affection occurs by paroxysms, with longer or shorter intervals between them, and of longer or shorter duration in different cases, and in the same case at different times.

It consists in a peculiar mode of inspiration, which it is difficult accurately to describe.

The child having had no apparent warning, is suddenly seized with a spasmodic inspiration, consisting of distinct attempts to fill the chest, between each of which a squeaking noise is often made: the eyes stare, and the child is evidently in great distress; the face and extremities, if the paroxysms continue long, become purple, the head is thrown backward, and the spine is often bent, as in opisthotones; at length a strong expiration takes place, a fit of crying generally succeeds, and the child evidently much exhausted, often falls asleep.

In one of these attacks a child sometimes, but not frequently dies.

They usually occur many times in the course of a day, and are often brought on by straining, by exercise, and by fretting, and sometimes they come on from no apparent cause.

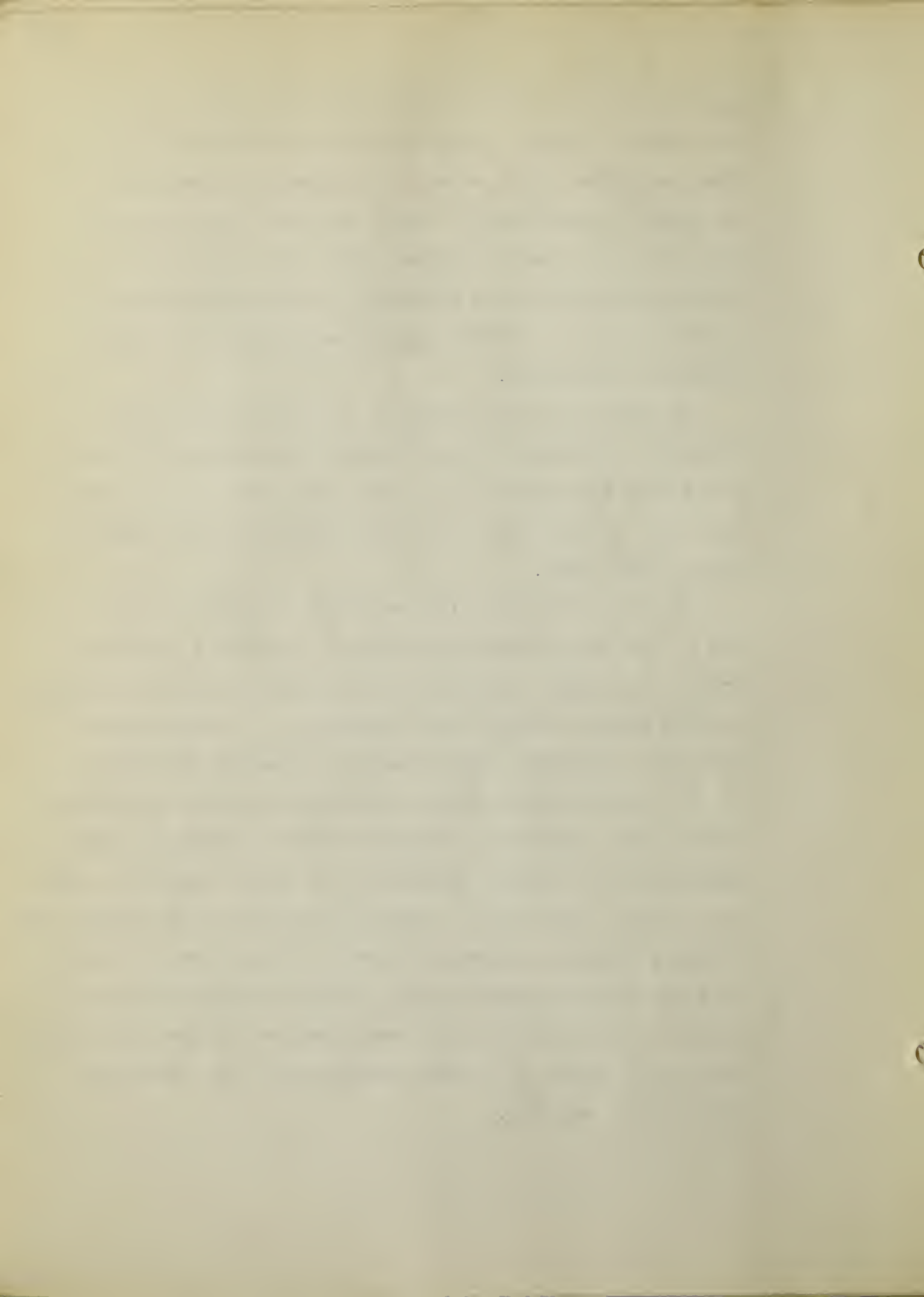
They very commonly take place after a full meal, and they often occur immediately upon waking from sleep, though be-

fore the time of waking the child had been lying in a most tranquil state. As the breathing is affected by these paroxysms, the complaint is generally referred to the organs of respiration, and it has been called chronic croup; but it is very different from croup; and is altogether of a convulsive character, arising from the same causes, and it is relieved by the same remedies as other convulsive affections.

Accompanying these symptoms, a bending of the toes downwards, clinching of the fists and the insertion of the thumbs into the palms of the hands, and bending the fingers upon them, is sometimes found, not only during the paroxysm, but at other times.

Clenching the fist with the thumb inserted into the palm of the hand, often exists for a long time in children, without being much observed, yet it is always to be considered an unfavourable symptom, and frequently is a forerunner of convulsive disorders, being itself a spasmodic affection.

It rarely happens that a child recovers from an attack of this sort, unless the progress of the disorder has been interrupted by a timely application of proper remedies, without a general convulsion. Then the friends become alarmed, and a disease which has existed for two or three months, is for the first time considered to be important enough to require medical assistance, after all the farago of popular medicines, such as fit drops, soot drops, assafoetida, &c. have been ineffectively applied.



Convulsions of this description seldom, if ever, occur after the expiration of the third year of a child's life, and not often in children which have lived by sucking till they have teeth, and have never taken animal food till the dentes cuspидati have come through the gums; this, however, is liable to some exception.

A long and very attentive consideration of this kind of convulsion, has led the writer to conclude, that in every case of convulsion (be the remote cause whatever it may) the brain at the time is organically affected, either directly or indirectly: directly when the convulsions arise from phrenitis, hydrocephalus, or on the sudden retiring of cutaneous eruptions, or of inflammation of the mucous membrane of the eyelids and eyes, or when they appear on the accession of some cutaneous disease, attended with febrile symptoms, especially scarlet fever, small-pox, and (sometimes, though less frequently,) of measles: indirectly, as when they are occasioned by an overloaded stomach or by indigestion, by peripneumony, by inflammation, or suppuration in the cavity of the pericardium, by glandular or other humors pressing on the large vessels leading to the lower extremities, or when they take place in the progress of infantile fever, or in marasmus.

Appendix B.Commercial Parathyroid Preparations Recognized by the
American Medical Association, 1932

From "New and Nonofficial Remedies" 1932

P. 315-319

Parathyroid Gland

Parathyroid preparations have been made from the dried gland for oral administration and by extracting substances from the gland for subcutaneous administration. The reports of success after oral therapy lack any conclusive evidence that this was dependent upon the use of the gland. No proof had been brought forward that the one definite effect that can be referred to the parathyroid gland (maintaining or raising the calcium concentration of the serum) has been produced by parathyroid preparations taken by mouth. To ascribe to the oral administration of parathyroid preparations improvement in conditions that are not definitely known to depend upon parathyroid disease, or deficiency, is illogical and misleading. In consideration of the accumulated evidence of the ineffectiveness of oral therapy with parathyroid, preparations of parathyroid designed for oral administration are not accepted for inclusion in this book. Recent investigations have shown that preparations which have a most powerful influence upon calcium metabolism may be made from the parathyroids of the ox. This substance is injected intramuscularly or subcutaneously. The calcium concentration of the serum of animals deprived of their parathyroid glands can be raised and maintained at a normal limit. By repeated doses it may

be raised far beyond this, either in parathyroidectomized or normal animals; unless the dosage is carefully regulated, death may ensue. The preparations can be standardized according to their activity in raising the lowered calcium concentration. Treatment by these parathyroid preparations is rational and has been shown to be of value in tetania parathyreopriva and in infantile tetany. A continuance of their use in the former condition is doubtless necessary. In infantile tetany their employment would appear to be a temporary expedient until other measures have an opportunity to combat the fundamental underlying condition. In gastric tetany, the calcium of the serum is normal. It is believed that its activity is interfered with. It has not yet been demonstrated sufficiently that this can be effected beneficially by parathyroid therapy.

The available clinical or scientific evidence does not permit an estimate of the ultimate usefulness of the parathyroid preparations. The near future should furnish evidence regarding their use in many different conditions. The danger of hypercalcemia, which is easily induced by overdosage with an active preparation makes it imperative that clinical studies should be carefully controlled by accurate determinations of the serum calcium.

PARA-THOR-MONE-LILLY. ----Parathyroid Extract-Collip.-

A stable, aqueous solution containing the active principle or principles of the parathyroid gland of cattle and having the property of relieving the symptoms of parathyroid

tetany and of increasing the calcium content of serum. It is standardized by its capacity to increase the blood serum calcium in normal dogs, one unit being defined as one one-hundredth of the amount of solution required to cause an increase of 0.005 gm. of calcium (Ca) in the blood serum of a twenty kilogram dog, the increase in calcium being determined fifteen hours after the injection of the solution.

Actions and Uses. -- Para-Thor-Mone-Lilly relieves the tetany of parathyroidectomized dogs and by its continued daily administration in small amounts further attacks can be prevented. Experiments with animals show, however, that frequently repeated small doses are cumulative and may raise the blood serum calcium to dangerous levels. It may be recognized that Para-Thor-Mone-Lilly is a most potent therapeutic agent and that its use may be attended with great danger unless due precautions are taken to avoid overdosage and the consequent development of hypercalcemia.

Para-Thor-Mone-Lilly is claimed to be a specific in tetania parathyreopriva and to have relieved acute and chronic tetany following thyroidectomy, so-called idiopathic tetany and infantile tetany. The experimental use of Para-Thor-Mone-Lilly in conditions believed to be due to a low calcium content of the blood serum must be carried on with extreme caution.

Dosage - In cases of true tetany where all the classical symptoms are fully developed, twenty to thirty units of Para-Thor-Mone-Lilly may be administered. In severe cases,

if necessary, this dose may be repeated two or three times within the first twenty-four hours, and the dosage then diminished as indicated by the condition of the patient. Doses ranging from ten to twenty-five units daily have been found sufficient to prevent the recurrence of tetany in chronic cases.

Para-Thor-Mone-Lilly may be administered subcutaneously, intramuscularly or intravenously.

Manufactured by Eli Lilly & Co., Indianapolis, under license from the University of Alberta. U. S. patent applied for. U. S. trademark 209,753.

PARA-THOR-MONE-LILLY, P-20, 2 Cc: Each cc. contains 20 units.

Fresh parathyroid glands of animals from which fat and connective tissue have been removed are ground and extracted with a hot acidified solution. After maceration for five hours, the glands are separated and again extracted with a hot acidified solution. The united extractions are cooled and the separated fat is removed. Alkali is added to neutralize the liquid, and the precipitate which forms at the neutral point is removed by filtration and dissolved in acidified water (pH 2.5). The hydrogen ion concentration of the solution is then adjusted to approximately pH 7.0 and the precipitate is again formed. This precipitate is dissolved in slightly acidified water, diluted approximately to the desired potency, filtered through a Berkefeld filter and submitted to standardization and sterility tests.



Parathyroid Hormone-Squibb. - A stable, aqueous solution containing the active principle or principles of the bovine parathyroid glands and having the property of relieving the symptoms of parathyroid tetany and of increasing the calcium content of the blood serum. It is standardized physiologically so that each cubic centimeter contains 20 units as defined by J. B. Collip, one unit being 1/100 the amount necessary to increase by 5 mg. the blood serum calcium from 100 cc. of blood at the end of fifteen hours in a normal dog weighing 20 kg.

Actions and Uses. - Parathyroid hormone-Squibb is specific for the tetany of normal or parathyroidectomized animals and is claimed to be equally specific for normal or parathyroidectomized man when injected subcutaneously for increasing the level of the blood serum calcium. It has been reported to be of value in infantile or maternal tetany, in lead poisoning, in idiopathic menstrual bleeding, in hemorrhage, and in relief of certain symptoms of tuberculosis. Due precaution should be taken to avoid the dangers of hypercalcemia that result from overdosage or from the continued administration of small doses.

Dosage. - Parathyroid hormone-Squibb is administered subcutaneously, the dosage varying with the severity of the condition in which it is used and with the individual to whom it is administered. In chronic parathyroid tetany as much as 30 units, repeated if necessary two or three times in the first twenty-four hours is suggested. After

symptoms have cleared up, one injection every second day is considered adequate. In infantile tetany an initial dose of 10 units, followed by a similar dose if convulsions are not relieved, has been reported to be successful.

Manufactured by E. R. Squibb & Sons, New York, No U. S. patent or trademark.

PARATHYROID HORMONE-SQUIBB, 5 CC.: Each cubic centimeter contains 20 units.

Parathyroid Hormone-Squibb is prepared from fresh bovine parathyroid glands. The glands are minced and then digested by boiling with diluted hydrochloric acid. The insoluble residue is removed and the solution purified by fractionation with alcohol, acetone and ether. Final separation of the active principle is effected by iso-electric precipitation, the resultant product containing a minimum of pigmentary impurities and inert protein. The finished product is filtered, standardized physiologically, and adjusted to contain the desired number of Collip units.

PAROIDIN. - Parathyroid Extract - Hanson. An aqueous solution containing the active principle or principles of the parathyroid glands of cattle and having the property of relieving the symptoms of parathyroid tetany and of increasing the calcium content of blood serum. It is standardized by its capacity to increase the blood serum calcium in parathyroidectomized dogs: one Hanson unit being defined

as one one hundredth the amount of solution necessary to produce an increase of 0.001 Gm. of calcium (Ca) in the blood serum of parathyroidectomized dogs weighing approximately 15 Kg., the increase being determined after administrations to dogs (twenty-four hours after operation) of a sufficient quantity of solution to cause an average increase in blood serum calcium of 3 mg. within 6 hours.

Actions and Uses. - Paroidin is of pronounced and definite value in the treatment of tetany. It has been used experimentally, but with inconclusive results, in a number of other conditions, such as chorea, gastric and duodenal ulcers, and delayed healing of wounds. To guard against the serious consequences of hyperparathyroidism, excessive doses of paroidin must be avoided and large doses of the preparation must not be administered without determination of the blood serum calcium.

Dosage. - The average adult dose of paroidin is 0.2 to 0.4 cc. (30-50 Hanson units) every twelve hours for five or six days, never more than ten days in succession. Treatment should then be discontinued for a week or two, to be resumed if necessary. For children the initial dose should not exceed 0.1 to 0.2 cc. (15 to 30 Hanson units).

Paroidin is administered subcutaneously or intramuscularly; not intravenously.

Manufactured by Parke, Davis & Co., Detroit. U. S. patent applied for. U. S. trademark.

The first part of the paper discusses the importance of the study of the history of the United States. It is argued that a knowledge of the past is essential for a proper understanding of the present. The author then proceeds to a detailed examination of the various factors which have shaped the development of the country. He considers the influence of the geographical situation, the character of the population, and the course of the political and social evolution. The paper concludes with a summary of the main points and a statement of the author's conclusions.

The second part of the paper is devoted to a critical analysis of the various theories which have been advanced to explain the development of the United States. The author examines the views of the leading writers on the subject, and attempts to show the strengths and weaknesses of each. He then presents his own theory, which is based on a combination of the various factors mentioned in the first part of the paper. The paper ends with a brief statement of the author's conclusions.

Paroidin, 5 cc. Each cubic centimeter contains 150 Hanson units.

Fresh bovine parathyroid glands from which fat and connective tissue have been removed are ground and extracted with dilute hydrochloric acid (approximately 0.5 per cent) at the boiling temperature for about one hour. The mixture is then chilled, filtered to remove fat, and the filtrate treated with an aqueous solution of trinitrophenol to precipitate the active principle together with some protein. The precipitate is collected and extracted with acetone and alcohol containing hydrochloric acid. An excess of acetone is then added to precipitate the active fraction in the form of a water-soluble powder, which is then redissolved in water diluted to the proper potency, sterilized, and submitted to standardization and sterility tests.

Appendix C.

The Determination of Serum Calcium by the Clark-Collip Modification of the Kramer-Tisdall Method.

Journal of Biological Chemistry, Vol. 63, 1925, p. 461 et seq.

2 cc. distilled water and 2 cc. unhemolyzed serum are placed in a very carefully cleaned graduated centrifuge tube and rotated until well mixed. 1 cc. saturated ammonium oxalate is added and the tube allowed to stand half hour until the precipitation is complete. The tube is then centrifuged for ten minutes at 1500 R.P.M. and the supernatant fluid carefully poured off. The mouth of the tube is wiped with clean gauze and the tube drained by inverting on clean filter paper for five minutes, when the mouth is again wiped.

The precipitate is stirred up and washed by directing a fine stream of ammonia water into the tube to the amount of 3 cc. using a syringe. It is centrifuged for ten minutes and drained as before. 2 cc. normal sulfuric acid is added and the tube placed in boiling water for one minute. It is titrated with hundredth normal potassium permanganate to a definite and persistent pink which will persist for one minute, using a microburette. A blank is run with normal sulfuric acid to determine the color of end point.

Calculation.

1 cc. hundredth normal permanganate is equivalent to 0.2 mg. calcium. Therefore $\frac{100 \times .2 \times X}{2} = \text{mgs. Ca/100 cc.}$

1891

My dear Mr. [Name]

I have just received your letter of the 14th inst.

and am glad to hear that you are well.

I am writing you a few lines to let you know

that I have received your letter of the 14th inst.

and am glad to hear that you are well.

I am writing you a few lines to let you know

that I have received your letter of the 14th inst.

and am glad to hear that you are well.

I am writing you a few lines to let you know

that I have received your letter of the 14th inst.

and am glad to hear that you are well.

I am writing you a few lines to let you know

that I have received your letter of the 14th inst.

x is the number of cc. permanganate used. It should be standardized for each determination against hundredth normal sodium oxalate.

Appendix D.A Case of Parathyroid Tetany Occurring after Thyroidectomy with Associated Behavior Problems and in Which Grafted Tissue was Ineffective.

The patient, Delia R., was a fourteen year old female, a ward of the Girls' Parole Board of the Massachusetts Department of Public Welfare, to whose care she had been committed following a series of sex misdemeanours and disorderly episodes. The home situation was complex, there being a stepmother with whom the patient did not get along. There were ten siblings and the patient was the seventh in the group. She had had gonorrhea, tonsillitis, measles and chorea.

After running away several times, she was committed to the Industrial School for Girls at Lancaster, March 31, 1931. There she was reported to be sly, stubborn and underhanded, lacking in ambition. She grew less and less amenable until she was considered to be a thoroughly self-centered and insubordinate girl.

On August 5, 1932, it was necessary to take her to the Massachusetts General Hospital because of increasing restlessness, loss of weight, excessive appetite, vomiting and palpitation on exertion. A diagnosis was made on examination of exophthalmic goiter because of typical prominence of the eyes, stare, lid lag and enlarged thyroid. The gland was firm, smooth and showed a thrill and bruit. The heart was slightly enlarged, rapid and forceful. There was a systolic murmur at the apex. Basal Metabolic

rate was plus 27 to plus 30. With iodine therapy, it dropped to 0 and a subtotal thyroidectomy was done. No evidence of parathyroid tetany was seen post-operatively. While in the hospital she was very uncooperative with doctors and nurses, refused to talk and was unduly introspective.

A month later she returned to the hospital with typical symptoms of parathyroid tetany; paraesthesia, pains in the extremities, carpal spasms, laryngeal stridor, positive Chvostek and Trousseau signs. There was no evidence of myxedema. Urine and blood morphology were normal. Serum calcium was 3.9 mg/100 cc. and the phosphorus was 10 mg./100 cc.

The day of entry she had a piece of parathyroid tumor transplanted from another patient without apparent benefit. After a period of two weeks observation, she was started on calcium chloride medication by mouth and definite improvement noted. On October 24, 1932, the serum calcium was 7.4 mg./100 cc. and the phosphorus was 10.2 mg./100 cc.

In addition to an improvement in physical condition, her personality underwent a marked change following disappearance of hyperthyroidism. She became pleasant, cooperative, willing to stand much hardship and pain during the course of experimental study and very pleasant to her associates.

On return to Lancaster, she again became unruly and difficult to manage. It seemed inadvisable to keep her at the school longer and she was sent to the Boston Psychopathic Hospital for mental diagnosis.

On admission there, March 10, 1933, physical examination was essentially normal. During her stay, she showed very varied behavior. Most of the time she was quiet and cooperative and helped with the ward work. At other times she had severe temper tantrums in reaction to minor situations. She had several tetanic convulsions which could be controlled by giving calcium chloride by mouth. These convulsions could be controlled somewhat by suggestion. It was felt that she appreciated that she could induce such attacks by hyperventilating and did so to obtain attention.

Blood Wassermann was negative, smears were negative for gonorrhea. She had a Basal Metabolic rate of minus 3. Blood calcium values were the following:

March 15	6.24 mg./100 cc.
March 24	6.3 mg./100 cc.

Blood phosphorus:

March 15	7.1 mg./100 cc.
March 24	8.5 mg./100 cc.

Cerebrospinal fluid calcium:

March 24	3.9 mg./100 cc.
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Cerebrospinal fluid phosphorus:

March 24	5.0 mg.
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She was discharged on April 19, 1933 with a diagnosis of ---Without Psychosis, Mental Deficiency.

The case is cited herein because the clinical picture and course of the disease are typical of tetany and its response to treatment. The accompanying photographs show the typical carpal spasm.

It will probably be necessary to give this patient calcium in one form or another throughout her lifetime. Parathormone, it was found at the Massachusetts General Hospital, was inapplicable, since in the course of prolonged administration, her tolerance was raised to the point where further increases in dosage would be very dangerous. It was recommended on her discharge that she be given a low fat diet with high calcium content plus Haliver oil in the hope that it would decrease the excretion of calcium. (Calcium is excreted by the bowel as calcium soaps)

X-rays of the long bones and skull showed a small, bridged skull but were otherwise negative. No calcifications of the pineal or parathyroids were noted. The humeri were thin and rather faintly calcified and the femora thicker and more densely calcified. Dental examination showed an enamel defect.

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DEPARTMENT OF THE HISTORY OF ARTS

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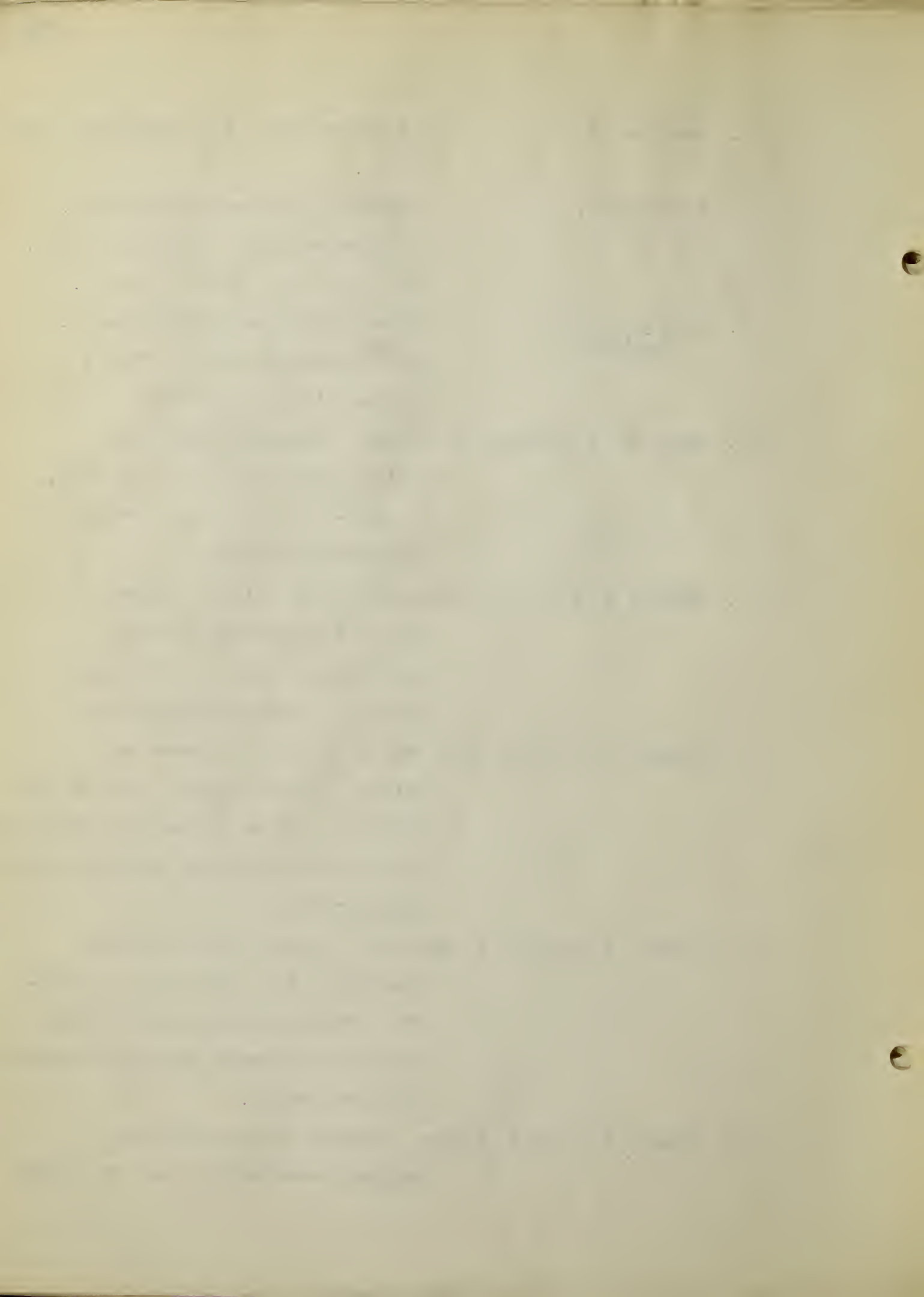


Figure Six D.R., aged 14

Figure Seven D.R., demonstrating carpal spasm

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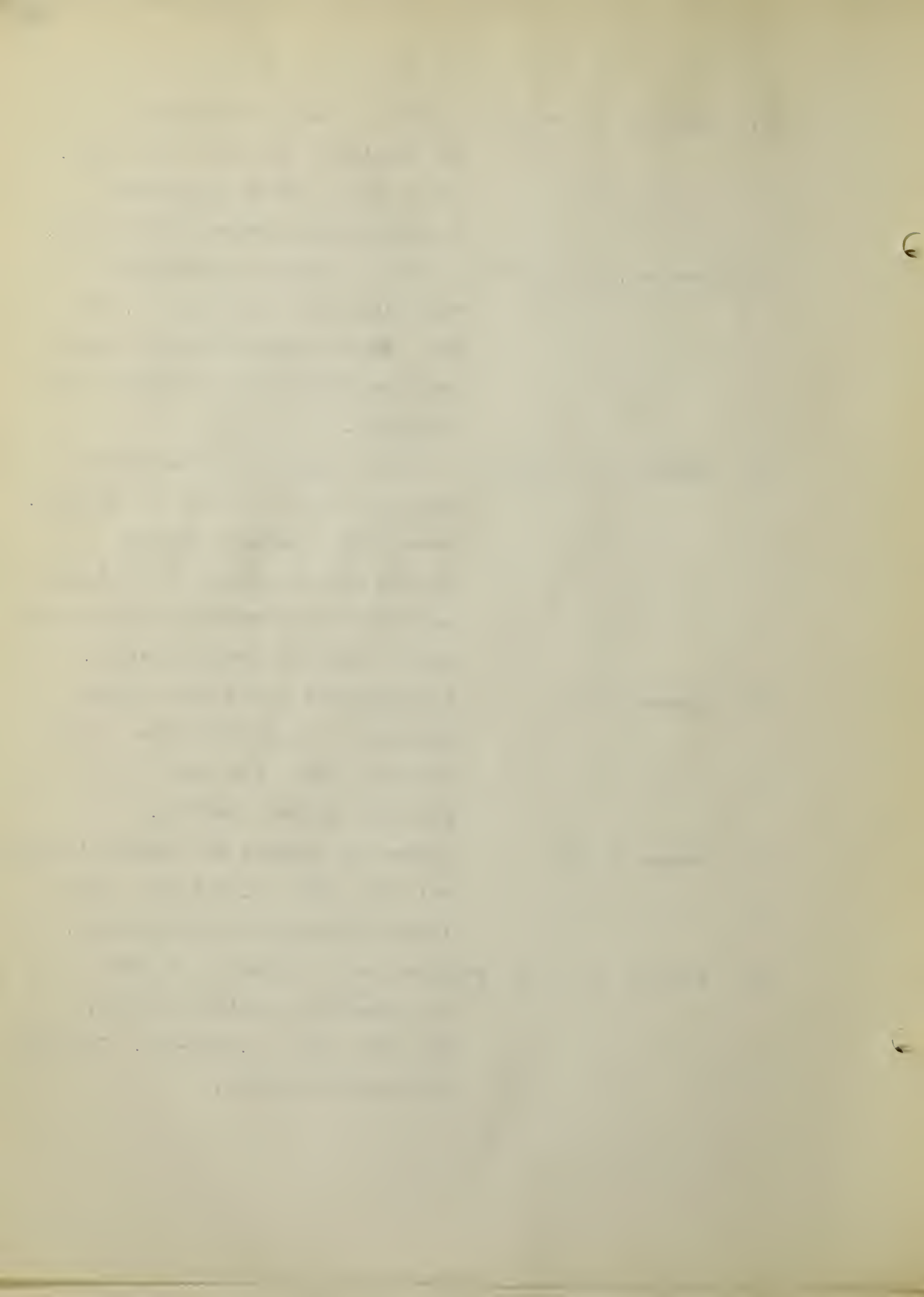
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which are satisfied by the functions $u_i(x, y, z)$ and $v_i(x, y, z)$ in the domain D of the space E_3 bounded by the surface S .

It is shown that the necessary conditions for the existence of solutions of the system of equations are satisfied in the case when the functions $u_i(x, y, z)$ and $v_i(x, y, z)$ are assumed to be continuous in the domain D and to satisfy the boundary conditions on the surface S .

The second part of the paper is devoted to a detailed study of the problem of the existence of solutions of the system of equations in the case when the functions $u_i(x, y, z)$ and $v_i(x, y, z)$ are assumed to be continuous in the domain D and to satisfy the boundary conditions on the surface S .

2. The second part of the paper is devoted to a detailed study of the problem of the existence of solutions of the system of equations

in the case when the functions $u_i(x, y, z)$ and $v_i(x, y, z)$ are assumed to be continuous in the domain D and to satisfy the boundary conditions on the surface S .

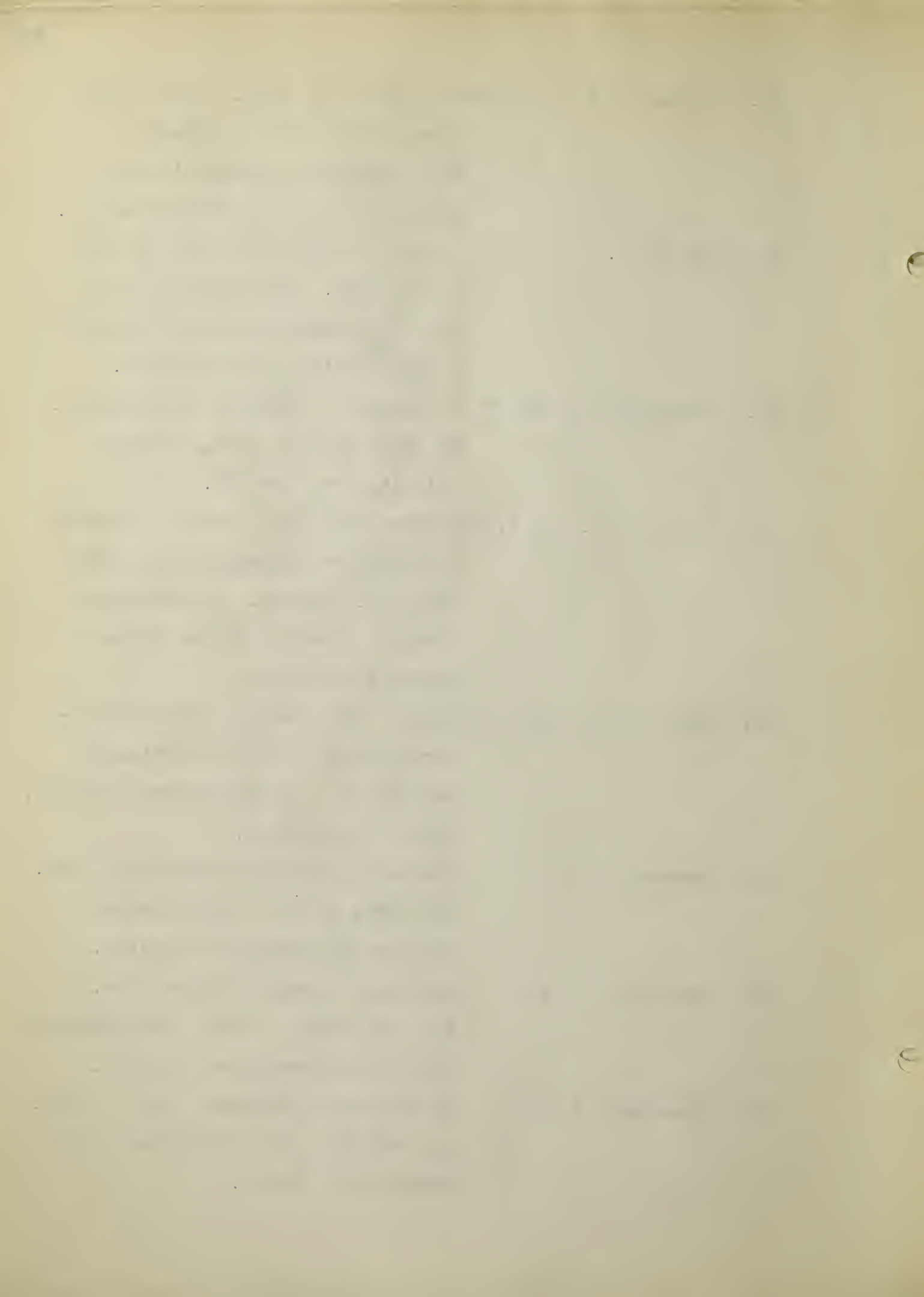
It is shown that the necessary conditions for the existence of solutions of the system of equations are satisfied in the case when the functions $u_i(x, y, z)$ and $v_i(x, y, z)$ are assumed to be continuous in the domain D and to satisfy the boundary conditions on the surface S .

The third part of the paper is devoted to a detailed study of the problem of the existence of solutions of the system of equations in the case when the functions $u_i(x, y, z)$ and $v_i(x, y, z)$ are assumed to be continuous in the domain D and to satisfy the boundary conditions on the surface S .

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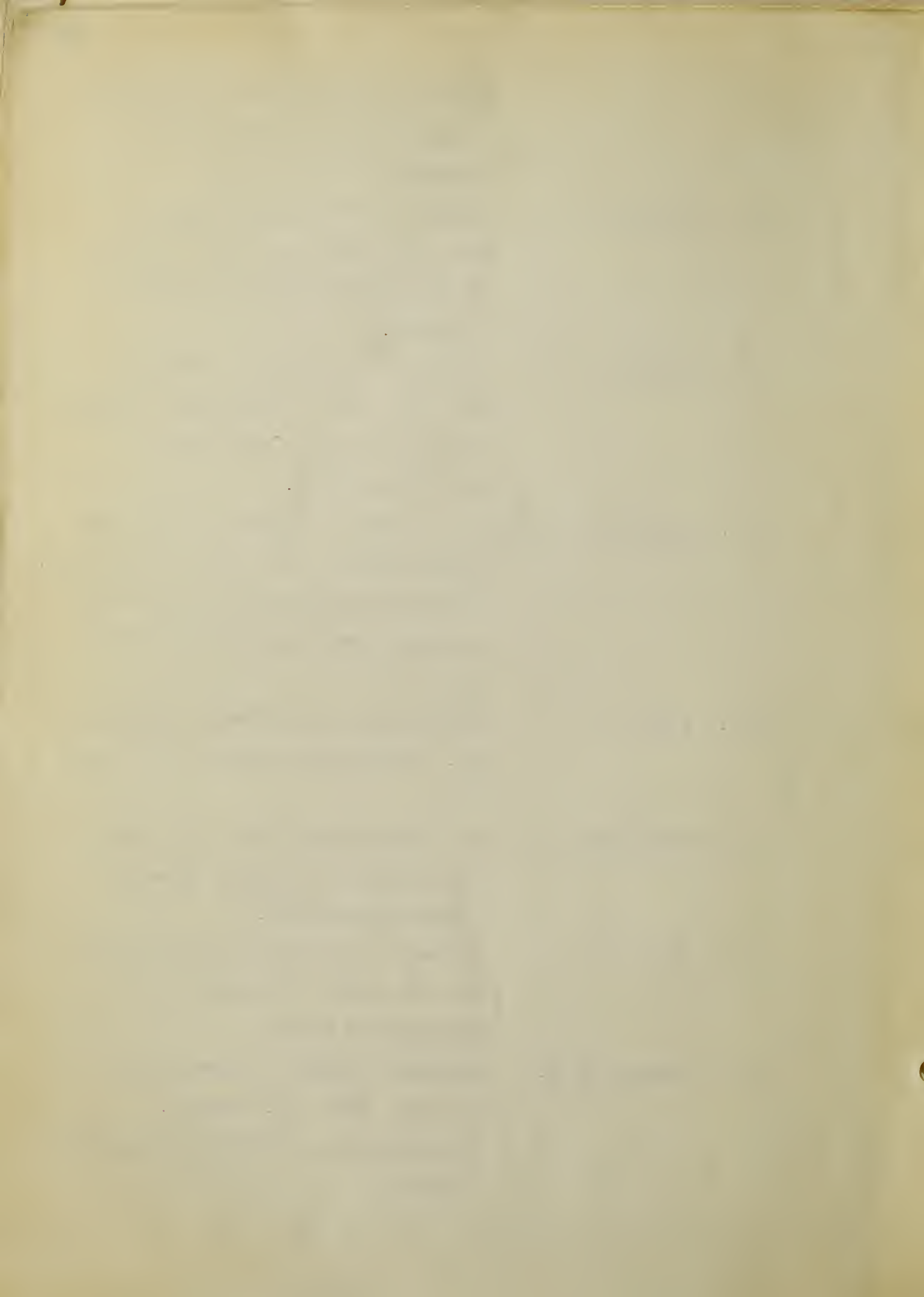


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